```
=> s EHNA
L1             1 EHNA

=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   51350-19-7  REGISTRY
CN   9H-Purine-9-ethanol, 6-amino-.beta.-hexyl-.alpha.-methyl-,
     (.alpha.R,.beta.S)-rel- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   9H-Purine-9-ethanol, 6-amino-.beta.-hexyl-.alpha.-methyl-, (R*,S*)-
OTHER NAMES:
CN   (.+-.)-Erythro-9-(2-Hydroxy-3-nonyl)adenine
CN   9-erythro-(2-Hydroxyl-3-nonyl)adenine
CN   EHNA
CN   erythro-9-(2-Hydroxy-3-nonyl)adenine
CN   erythro-9-(2-Hydroxyl-3-nonyl)adenine
CN   NSC 263165
FS   STEREOSEARCH
DR   79763-32-9
MF   C14 H23 N5 O
CI   COM
LC   STN Files:   AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CEN,
       CHEMCATS, CSCHEM, DDFU, DRUGU, IPA, MSDS-OHS, TOXCENTER, USPAT2,
       USPATFULL
         (*File contains numerically searchable property data)

Relative stereochemistry.
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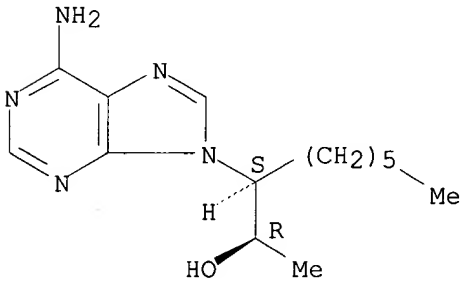


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             227 REFERENCES IN FILE CA (1967 TO DATE)
               3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             228 REFERENCES IN FILE CAPLUS (1967 TO DATE)


=> file embase biosis medline caplus uspatfull
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
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FILE 'CAPLUS' ENTERED AT 19:16:29 ON 14 MAY 2002
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=> s EHNA or 51350-19-7/rn
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L2 1406 EHNA OR 51350-19-7/RN

=> s dementia or memory or alzheimer's or parkinson's or depression or degeneration or stroke or trauma
3 FILES SEARCHED...
L3 1978222 DEMENTIA OR MEMORY OR ALZHEIMER'S OR PARKINSON'S OR DEPRESSION OR DEGENERATION OR STROKE OR TRAUMA

=> s l2 and l3
L4 87 L2 AND L3

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 64 DUP REM L4 (23 DUPLICATES REMOVED)

=> s l5 and py<2000
2 FILES SEARCHED...
L6 37 L5 AND PY<2000

=> d l6 1-10 ab bib

L6 ANSWER 1 OF 37 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB We investigated whether adenosine neuromodulation is involved in a benzodiazepine (midazolam)-induced **depression** of excitatory synaptic transmissions in the CA1 and dentate gyrus (DG) regions in rat hippocampal slices. Field excitatory postsynaptic potentials (fEPSPs), evoked by electrical stimulation of the CA1-Schaffer collateral or the DG-perforant path, were recorded with extracellular microelectrodes from CA1-stratum radiatum or DG-stratum moleculare in oxygenated ACSF. The initial slope of the fEPSPs was analyzed for assessing the drug effects. Midazolam (1 .mu.M) transiently depressed CA1- and DG-fEPSPs. The fEPSPs were depressed to approximately 75% of the control values, and then gradually recovered. The **depression** was not affected by bicuculline, a GABA(A) receptor antagonist, although it was completely antagonized by aminophylline, an adenosine receptor antagonist. Dipyridamole (5 .mu.M), an adenosine uptake inhibitor, depressed the fEPSPs in a similar manner to midazolam. An adenosine deaminase inhibitor, **EHNA**, also transiently depressed the fEPSPs, but in a different manner. Exogenous adenosine persistently depressed the fEPSPs. The effects of the drugs were not significantly different in the CA1 and DG regions. The results suggest that midazolam (1 .mu.M) depresses excitatory synaptic

transmission through the adenosine neuromodulatory system by inhibiting adenosine uptake in the CA1 and DG regions of the hippocampus.
AN 1999105035 EMBASE
TI Involvement of the adenosine neuromodulatory system in the benzodiazepine-induced **depression** of excitatory synaptic transmissions in rat hippocampal neurons in vitro.
AU Narimatsu E.; Aoki M.
CS E. Narimatsu, Department of Physiology, Sapporo Medical University, School of Medicine, South 1, West 17, Chuo-ku, Sapporo, Hokkaido 060-0061, Japan.
enarimat@sapmed.ac.jp
SO Neuroscience Research, (1999) 33/1 (57-64).
Refs: 23
ISSN: 0168-0102 CODEN: NERADN
PUI S 0168-0102(98)00110-2
CY Ireland
DT Journal; Article
FS 008 Neurology and Neurosurgery
024 Anesthesiology
030 Pharmacology
037 Drug Literature Index
LA English
SL English

L6 ANSWER 2 OF 37 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB In adult mammalian cardiomyocytes, stimulation of muscarinic receptors counterbalances the .beta.-adrenoceptor-mediated increase in myocardial contractility and heart rate by decreasing the L-type Ca2+ current (I(Ca)) (1, 2). This effect is mediated via inhibition of adenylyl cyclase and subsequent reduction of cAMP-dependent phosphorylation of voltage-dependent L-type Ca2+ channels (3). Little is known, however, about the nature and origin of this pivotal inhibitory pathway. Using embryonic stem cells as an in vitro model of cardiomyogenesis, we found that muscarinic agonists depress I(Ca) by 58 .+-.3% (n=34) in early stage cardiomyocytes lacking functional .beta.- adrenoceptors. The cholinergic inhibition is mediated by the nitric oxide (NO)/cGMP system since it was abolished by application of NOS inhibitors (L- NMA, L-NAME), an inhibitor of the soluble guanylyl cyclase (ODQ), and a selective phosphodiesterase type II antagonist (**EHNA**). The NO/cGMP-mediated I(Ca) **depression** was dependent on a reduction of cAMP/protein kinase A (PKA) levels since application of the catalytic subunit of PKA or of the PKA inhibitor PK) prevented the carbachol effect. In late development stage cells, as reported for ventricular cardiomyocytes (2, 4), muscarinic agonists had no effect on basal I(Ca) but antagonized .beta.-adrenoceptor-stimulated I(Ca) by 43 .+-.4% (n=16). This switch in signaling pathways during development is associated with distinct changes in expression of the two NO-producing isoenzymes, eNOS and iNOS, respectively. These findings indicate a fundamental role for NO as a signaling molecule during early embryonic development and demonstrate a switch in the signaling cascades governing I(Ca) regulation.
AN 1999056293 EMBASE
TI Regulation of the L-type Ca2+ channel during cardiomyogenesis: Switch from NO to adenylyl cyclase-mediated inhibition.
AU Ji G.J.; Fleischmann B.K.; Bloch W.; Feelisch M.; Andressen C.; Addicks

K.; Hescheler J.
CS J. Hescheler, Institut fur Neurophysiologie, Universitat zu Koln, Robert-Koch-Str. 39, D-50931 Koln, Germany. jh@physiologie.uni-koeln.de
SO FASEB Journal, (1999) 13/2 (313-324).
Refs: 48
ISSN: 0892-6638 CODEN: FAJOEC
CY United States
DT Journal; Article
FS 021 Developmental Biology and Teratology
029 Clinical Biochemistry
LA English
SL English

L6 ANSWER 3 OF 37 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB Background: There has been increasing interest in the development of agents that utilize endogenous adenosine to exert their actions. We tested the hypothesis that substances that either potentiate the activity (allosteric enhancers) or increase the interstitial concentration (inhibitors of metabolism) of endogenous adenosine may cause event (tachycardia)-specific **depression** of AV nodal conduction. Methods and Results: The frequency- dependent effects of iodotubereidin (ITU, an inhibitor of adenosine kinase), erythro-9-(2-hydroxy-3-nonyl)adenine (**EHNA**, an inhibitor of adenosine deaminase), draflazine (a nucleoside transport blocker), and PD81,723 (an allosteric enhancer of the A1 adenosine receptor binding) on the stimulus- to-His bundle (SH) interval, a measure of AV nodal conduction, were determined in guinea pig hearts and compared with those of adenosine and diltiazem. All drugs depressed AV nodal conduction in a frequency-dependent manner. The ratios of SH interval prolongations at fast to slow pacing rates for draflazine, ITU+**EHNA**, PD81,723 adenosine, and diltiazem were 17.5.+-.3.4, 11.1.+-.5.0, 3.5.+-.0.9, 10.1.+-.2.8, and 8.3.+-.3.5, respectively. Coincident with the prolongation of the SH interval at rapid pacing rates, draflazine and ITU+**EHNA** increased the epicardial fluid adenosine concentrations by 2.2- and 2.6-fold, respectively. In contrast, epicardial transudate levels of adenosine do not change in the presence of PD81,723. The AV nodal effects of draflazine, ITU, **EHNA**, and PD81,723 were reversed by the A1 adenosine receptor antagonist 8-cyclopentyltheophylline and adenosine deaminase, implicating endogenous adenosine acting at the A1 adenosine receptor. Conclusions: Adenosine-regulating agents that act in an event- and site- specific manner represent a novel drug design strategy that may potentially be valuable for the long-term treatment of supraventricular arrhythmias and control of ventricular rate during atrial fibrillation or flutter.
AN 96368436 EMBASE
DN 1996368436
TI Modulation of atrioventricular nodal function by metabolic and allosteric regulators of endogenous adenosine in guinea pig heart.
AU Dennis D.M.; Raatikainen M.J.P.; Martens J.R.; Belardinelli L.
CS Department of Medicine, University of Florida, JHMHC, 1600 SW Archer Rd,Gainesville, FL 32610, United States
SO Circulation, (1996) 94/10 (2551-2559).
ISSN: 0009-7322 CODEN: CIRCAZ
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry

030 Pharmacology
037 Drug Literature Index
LA English
SL English

L6 ANSWER 4 OF 37 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB Background: Although myocardial ATP is essential for myocardial viability and ventricular function, it is a major source of free radical substrates for endothelial xanthine oxidase. Correlation between myocardial ATP and ventricular function has been hindered by the impact of ATP catabolites on ventricular function during reperfusion. Objectives: This work results from four separate experiments assessing the role of nucleoside efflux in reperfusion mediated injury to determine the dual role of myocardial ATP in postischemic ventricular dysfunction. An adenosine deaminase inhibitor, erythro-9-(2-hydroxy-3-nonyl)adenine (**EHNA**), and an adenine nucleoside transport blocker, p-nitrobenzylthioinosine (NBMPR), were used to specifically inhibit adenosine deamination and block nucleoside release, respectively. This pharmacological intervention results in site-specific entrapment of intramyocardial adenosine and inosine, generated during ischemia, and blocks degradation to free radical substrates during reperfusion, thereby limiting the impact of reperfusion mediated injury. Methods: Forty-three anesthetized dogs were instrumented to monitor left ventricular performance from the slope of the relationship between **stroke** work and end-diastolic length (SW/EDL). Hearts were subjected to varying periods (30, 60, or 90 min) of global ischemia and 60 or 120 minutes of reperfusion. Two control groups for 30 and 60 minutes of ischemia (16 dogs) received only saline solution. Four treated groups (27 dogs) received saline containing 100 .mu.M **EHNA** and 25 mM NBMPR prior to ischemia or only during reperfusion (n = 7). Myocardial biopsies were analyzed for ATP catabolites and NAD+. Results: Myocardial ATP and left ventricular function were severely depressed by 50% and 80% in the untreated controls, following 30 and 60 minutes of ischemia (37.degree.C), respectively. Ventricular dysfunction was inversely related to inosine levels in the myocardium at the end of the ischemic period. Administration of **EHNA**/NBMPR before ischemia or only during reperfusion resulted in significant accumulation of mainly adenosine or inosine, respectively. Entrapment of nucleosides was associated with complete recovery of ventricular function after 30 or 60 minutes of ischemia. Hearts subjected to 90 minutes of ischemia developed contracture. Conclusions: Despite severely reduced ATP levels, ventricular function significantly recovered to preischemic values only in the **EHNA**/NBMPR-treated groups. Selective blockade of purine release during reperfusion is cardioprotective against postischemic reperfusion mediated injury. It is concluded that nucleoside transport plays an important role in regulation of endogenous adenosine and inosine affecting the degree of myocardial injury or protection from reperfusion mediated injury.
AN 94182747 EMBASE
DN 1994182747
TI Separation between ischemic and reperfusion injury by site specific entrapment of endogenous adenosine and inosine using NBMPR and **EHNA**.
AU Abd-Elfattah A.S.; Wechsler A.S.
CS Department of Surgery, Medical College of Virginia, P.O. Box 532,Richmond,

VA 23298, United States
SO Journal of Cardiac Surgery, (1994) 9/3 SUPPL. (387-396).
ISSN: 0886-0440 CODEN: JCASE3
CY United States
DT Journal; Conference Article
FS 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English

L6 ANSWER 5 OF 37 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB Background. Metabolic interventions capable of preventing ventricular dysfunction 'stunning' or accelerating its functional recovery have potential clinical importance. Myocardial protection of the stunned myocardium has not been documented when drugs were administered only during postischemic reperfusion. The role of ATP depletion and release of purines in myocardial injury was assessed using the selective nucleoside transport blocker p- nitrobenzylthioinosine (NBMPR) in a combination with specific adenosine deaminase inhibitor erythro-9-[hydroxy-3-nonyl]adenine (**EHNA**) administered during reperfusion after reversible ischemic injury. Methods and Results. Sixteen anesthetized dogs were instrumented with minor axis sonocrystals and intraventricular Millar. Ventricular performance was determined, off bypass, from the slope of the relationship between **stroke**-work and end-diastolic length as a sensitive and load-independent index of contractility within physiological range. Hearts were subjected to 20 minutes' warm global ischemia and reperfused with warm blood treated with either saline (control group, n=8) or saline containing 100 .mu.mol/L **EHNA** and 25 .mu.mol/L NBMPR (**EHNA**/NBMPR-treated group, n=8). Myocardial biopsies were collected and analyzed for ATP and metabolites using high-performance liquid chromatography. Warm ischemia induced significant depletion of ATP (P<.05 versus preischemia) and accumulation of inosine at the end of ischemia (>90% of total nucleosides) in both groups. Complete functional recovery was observed in the **EHNA**/NBMPR-treated group (P<.05 versus control group). Conclusions. Selective entrapment of adenine nucleosides during postischemic reperfusion attenuated ventricular dysfunction (stunning) after brief global ischemia. It is concluded that nucleoside transport plays an important role in myocardial stunning, and its blockade augmented myocardial protection against reperfusion injury. Selective entrapment of endogenous inosine, generated during ischemia, represents an attractive therapeutic approach to the alleviation of postischemic dysfunction mediated by reperfusion in a wide spectrum of ischemic syndromes, including percutaneous transluminal coronary angioplasty and coronary artery bypass graft surgery.
AN 93324597 EMBASE
DN 1993324597
TI Protection of the stunned myocardium: Selective nucleoside transport blocker administered after 20 minutes of ischemia augments recovery of ventricular function.
AU Abd-Elfattah A.S.; Ding M.; Dyke C.M.; Wechsler A.S.
CS Department of Surgery, Medical College of Virginia, PO Box 532,Richmond, VA 23298-0532, United States
SO Circulation, (1993) 88/5 II (336-343).
ISSN: 0009-7322 CODEN: CIRCAZ

CY United States
DT Journal; Conference Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English

L6 ANSWER 6 OF 37 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB Using an extracellular recording technique, we have investigated the site of action of adenosine and muscarine on the rat superior cervical ganglion (SCG). The adenosine-induced hyperpolarization and muscarine-induced depolarization of ganglia were localized to the cell bodies of the ganglia. Responses to muscarine and adenosine were larger when recorded via the internal carotid nerve (ICN) compared with the external carotid nerve. **Depression** of the response to muscarine by adenosine was similar for both nerve trunks. The effects of adenosine and cyclic nucleotides on the d.c. potential and the depolarization to muscarine were examined by recording via the ICN. Adenosine at concentrations up to 1 mM produced concentration-dependent hyperpolarizations. Hyperpolarization induced by 100 .mu.M adenosine was unaffected by 1 .mu.M tetrodotoxin or the muscarinic M1-receptor antagonist pirenzepine (0.3 .mu.M). In contrast, hyperpolarizations to 100 .mu.M adenosine were significantly reduced by 10 .mu.M 8-phenytheophylline (55 .+-. 7 .mu.V vs 15 .+-. 9 .mu.V, $P < 0.01$, $n = 4$). Two agents known to increase intracellular cAMP, i.e. 8-bromocyclic-adenosine-3'-5'monophosphate (8BrcAMP) and isoprenaline, depolarized ganglia. Depolarizations to 100 nM mucarine were significantly depressed by adenosine (100 .mu.M) by 26 .+-. 2% ($n = 61$), but unaltered by 8BrcAMP or cyclic guanosine-3'-5'monophosphate. Dipyridamole and hydroxy-nitro-benzylthioguanosine (inhibitors of adenosine transport) and erythro-6-amino-9-(2-hydroxy-3-nonyl)adenine (**EHNA**, an inhibitor of adenosine deaminase), potentiated the **depression** by adenosine of the response to muscarine, and the hyperpolarization to adenosine respectively. However, there was no evidence to support the hypothesis that there was spontaneous release of endogenous adenosine under the conditions of study, as dipyridamole or **EHNA** did not alter the control d.c. potential or the depolarization to muscarine. It is concluded that the ability of adenosine to hyperpolarize and depress the response of the rat SCG to muscarine is due to the direct activation of postsynaptic somatodendritic P1-purinoceptors and unlikely to be mediated by an increase in intracellular cAMP. In addition the rat SCG has mechanisms for both the uptake and inactivation of adenosine.
AN 93163835 EMBASE
DN 1993163835
TI On the site of action and inactivation of adenosine by the rat superior cervical ganglion.
AU Connolly G.P.; Stone T.W.
CS Department of Physiology, University College, Gower Street,London WC1E 6BT, United Kingdom
SO Journal of Autonomic Pharmacology, (1993) 13/3 (237-247).
ISSN: 0144-1795 CODEN: JAPHDU
CY United Kingdom
DT Journal; Article
FS 002 Physiology
030 Pharmacology

037 Drug Literature Index
LA English
SL English

L6 ANSWER 7 OF 37 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB The aim of this study was to determine the dual role of ATP as an energy substrate and as a major source of oxygen-derived free-radical-mediated reperfusion injury by using adenine nucleoside blocker, p-nitrobenzylthioinosine (NBMPR), and adenosine deaminase inhibitor, erythro-9-(2-hydroxy-3-nonyl)adenine (**EHNA**). In a randomized study, 16 dogs were instrumented with minor-axis LTZ-piezoelectric crystals and intraventricular pressure transducers to monitor, off bypass, left ventricular performance by using a sensitive and load-independent index of contractility (slope of the **stroke** work-end-diastolic length relation). Hearts were subjected to 60 minutes of normothermic global ischemia and 120 minutes of reperfusion. Normal saline without (Group 1, n = 8) or with (Group 2, n = 8) NBMPR and **EHNA** was infused in three boluses into the cardiopulmonary bypass reservoir before ischemia and reperfusion. Transmural serial biopsies were obtained before and during ischemia and reperfusion and analyzed for myocardial adenine nucleotide pool intermediates by using high-performance liquid chromatography. In the control group, three hearts developed ischemic contracture and another three hearts exhibited cardiogenic shock during reperfusion. In the **EHNA**/NBMPR-treated group, left ventricular performance recovered within 30 minutes of reperfusion ($p < 0.05$ vs. control). Myocardial ATP was depleted to 20% of normal in both groups by the end of ischemia ($p < 0.05$). Intramyocardial adenosine in the **EHNA**/NBMPR-treated group was 12-fold greater (15.09 .+-. 1.6 nmol/mg protein) than the control group at the end of the ischemic period ($p < 0.05$). Inosine was about fourfold higher in the control group (19.07 .+-. 1.50 nmol/mg protein) compared with the drug-treated group ($p < 0.05$). During reperfusion, myocardial ATP levels increased to approximately 50% of normal in the **EHNA**/NBMPR group while remaining depressed (20% of normal) in the control group. Thus, despite the dramatic loss of myocardial ATP during ischemia, complete recovery of ventricular performance and significant repletion of ATP during reperfusion were observed when adenosine transport and deamination were modulated during ischemia and reperfusion. These results suggest that 1) the myocardium may have more ATP than is needed for basic cardiac functions and 2) washout of ATP diffusible catabolites is detrimental to ventricular performance during reperfusion. Specific blockade of nucleoside transport resulted in complete functional recovery despite low but critical ATP levels. It is concluded that adenine nucleoside transport regulates the release of free radical substrate precursors, thereby preventing ventricular dysfunction during reperfusion.
AN 90390714 EMBASE
DN 1990390714
TI Is adenosine 5'-triphosphate derangement or free-radical-mediated injury the major cause of ventricular dysfunction during reperfusion? Role of adenine nucleoside transport in myocardial reperfusion injury.
AU Abd-Elfattah A.S.; Jessen M.E.; Hanan S.A.; Tuchy G.; Wechsler A.S.
CS Department of Surgery, Medical College of Virginia, MCV Station Box 532,Richmond, VA 23298-0532, United States
SO Circulation, (1990) 82/5 SUPPL. (IV-341-IV-350).
ISSN: 0009-7322 CODEN: CIRCAZ
CY United States
DT Journal; Article
FS 002 Physiology

018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LA English
SL English

L6 ANSWER 8 OF 37 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB Alteration of membrane fluidity during enzymatic methylation of membrane phosphatidylethanolamine (PE) and neutralization of negative charges of membrane proteins due to methylation of carboxyl groups may contribute to sperm motility. Therefore, enzymatic phospholipid methylation and carboxymethylation, and the consequences of their inhibition on motility, were studied using human sperm. These studies gave the following results. Human sperm homogenates contained two phospholipid N-methyltransferases (PMT) which converted PE to phosphatidylcholine (PC) in the presence of S-adenosylmethionine (SAM). The first PMT converted PE to phosphatidyl-N-methylethanolamine (PME). It had a K(m) of 4.0 .mu.M and a pH optimum of 8.0. The second PMT converted PME to phosphatidyl-N,N-dimethylethanolamine and PC. It had a K(m) of 71 .mu.M and a pH optimum of 10.0. Spermatozoa also contained protein carboxymethylase (PCM) and methyl acceptor protein (MAP). The intracellular levels of S-adenosylhomocysteine (SAH), an inhibitor of SAM-mediated methylations, were increased by adding adenosine (100 .mu.M), L-homocysteine thiolactone (L-HCT, 10 .mu.M), and erythro-9-(2-hydroxy-3-nonyl)-adenine (**EHNA**, 10 .mu.M), an inhibitor of adenosine deaminase, to human sperm ejaculates that had been diluted with sodium phosphate buffer at pH 7.4 and 25.degree.. The motility index of each sperm suspension was determined every hour for 4 hr. In the presence of the mixture of adenosine, L-HCT and **EHNA**, the motility index was depressed by 57%. Under similar conditions, phospholipid methylation was depressed by 48%. Similar experiments were also conducted in the presence of 3-deazaadenosine (Deaza, 80 .mu.M), a selective inhibitor of SAH hydrolase. In the presence of adenosine and L-HCT, Deaza depressed the motility index by 60% and phospholipid methylation by 86%. The potencies of SAH in the inhibition of phospholipid methylation and protein carboxymethylation in sperm homogenates had the following order: PMT I > PCM > PMT II. These observations indicate that the PMT system and/or the PCM-MAP system play a significant role in the regulation of human sperm motility.
AN 83157824 EMBASE
DN 1983157824
TI **Depression** of human sperm motility by inhibition of enzymatic methylation.
AU Rama Sastry B.V.; Janson V.E.
CS Dep. Pharmacol., Vanderbilt Univ. Sch. Med., Nashville, TN 37232, United States
SO Biochemical Pharmacology, (1983) 32/8 (1423-1432).
CODEN: BCPCA6
CY United Kingdom
DT Journal
FS 037 Drug Literature Index
030 Pharmacology
029 Clinical Biochemistry
028 Urology and Nephrology
LA English

L6 ANSWER 9 OF 37 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1994:471159 BIOSIS
DN PREV199497484159
TI The adenosine deaminase inhibitor, **EHNA**, provides CA1 neuroprotection from **trauma**, hypoxia and nitric oxide.
AU Girard, J. M. (1); Panizzon, K. L.; Parsons, J.; Wallis, R. A.
CS (1) Dep. Neurol., UCLA, Los Angeles, CA 90024 USA
SO Society for Neuroscience Abstracts, (1994) Vol. 20, No. 1-2, pp. 192. Meeting Info.: 24th Annual Meeting of the Society for Neuroscience Miami Beach, Florida, USA November 13-18, 1994
ISSN: 0190-5295.
DT Conference
LA English

L6 ANSWER 10 OF 37 MEDLINE
AB We investigated whether xanthine oxidase-derived superoxide radical generation could be modified by interfering with adenosine transport and metabolism in reducing myocardial injury during post-ischemic reperfusion.
Isolated rat hearts perfused at constant pressure were subjected to 20 min of pretreatment with test agents, followed by 40 min global ischemia and 30 min reperfusion with or without test agents. In hearts treated with adenosine deaminase inhibitor, erythro 9-(2-hydroxy-3-nonyl) adenine (**EHNA**), alone or together with a selective nucleoside transport blocker, p-nitrobenzylthioinosine (NBMPR), the accumulated amount of O-2. was significantly reduced [10.2+/-0.97, 11.6+/-2.4, 8.1+/-0.51, respectively, v 31.6+/-2.1 (s. e.) nmol/wet g/30 min in ischemic control, P<0.01]. A positive correlation between O-2. and inosine release was observed in the initial 5 min of reperfusion in hearts treated with either **EHNA** or NBMPR (r=0.475, P<0.05). Furthermore, the accumulated amount of LDH release showed positive correlation with that of O-2. among the same groups (r=0.474, P<0.05). Both **EHNA** and NBMPR had the cardioprotective effect on the recovery of left ventricular end-diastolic pressure (LVEDP), ATP repletion, and build up of endogenous adenosine. This study suggests that : (1) adenosine metabolism can be manipulated towards the formation of O-2. during reperfusion, and it has an important bearing on the cardiac recovery of ischemic myocardium, (2) the generation of O-2. is related to only inosine release during initial reperfusion.

AN 1998443527 MEDLINE
DN 98443527 PubMed ID: 9769236
TI Modulation of adenosine effects in attenuation of ischemia and reperfusion injury in rat heart.
AU Hirai K; Ashraf M
CS Department of Pathology and Laboratory Medicine, University of Cincinnati Medical Center, Cincinnati, OH, 45267, USA.
NC HL-23597 (NHLBI)
SO JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY, **(1998 Sep)** 30 (9) 1803-15.
Journal code: J72; 0262322. ISSN: 0022-2828.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199811
ED Entered STN: 19990106
Last Updated on STN: 19990106

Entered Medline: 19981119

=> d 11-27 ab bib

L6 ANSWER 11 OF 37 MEDLINE

AB This study 1) compares the negative chronotropic and dromotropic actions of adenosine in guinea pig, rat, and rabbit hearts; 2) investigates the mechanism(s) for the different responses; and 3) determines the physiological implications. Isolated perfused hearts were instrumented for measurement of atrial rate and atrioventricular (AV) nodal conduction time. Differences in metabolism of adenosine were determined in the absence and presence of dipyridamole (nucleoside uptake blocker) and erythro-9-(2-hydroxy-3-nonyl)adenine (**EHNA**, adenosine deaminase inhibitor). Dipyridamole plus **EHNA** decreased adenosine's EC50 for the negative dromotropic effect by 14-fold in guinea pig heart and 1.6-fold in rat heart. This is consistent with the greater number of [3H]nitrobenzylthioinosine binding sites measured in membranes from guinea pig (1,231 +/- 68 fmol/mg protein) compared with rat (302 +/- 31 fmol/mg protein) and rabbit (260 +/- 28 fmol/mg protein) atria. The potency of adenosine to slow atrial rate and prolong AV nodal conduction time was greater in guinea pig than in rat or rabbit hearts. This rank order of potency correlated well with the number of binding sites for the specific adenosine receptor radioligand 125I-aminobenzyladenosine in guinea pig (102 +/- 13 fmol/mg protein), rat (11 +/- 0.5 fmol/mg protein), and rabbit (8 +/- 1 fmol/mg protein) atrial membranes. Hypoxia increased the rate of adenosine release by severalfold and caused slowing of heart rate and AV block. In spontaneously beating hearts, the main effect of hypoxia was a slowing of ventricular rate, which in the guinea pig heart was due to AV block and in the rat heart to atrial slowing. In atrial paced hearts, hypoxia caused a marked prolongation of AV nodal conduction time in guinea pig (39 +/- 4 msec) and rabbit (29 +/- 5 msec) hearts, but only small effect in rat hearts (10 +/- 2 msec). The differences in response to hypoxia could be accounted for by the species-dependent differences in the 1) amount of adenosine released and metabolized, 2) sensitivity of the hearts to adenosine, and 3) dependency of AV nodal conduction on atrial rate. The findings indicate that the results from physiological or pharmacological studies on adenosine in one species may not be applicable to others, and the ultimate effect of adenosine and hypoxia is to slow ventricular rate.

AN 91004685 MEDLINE

DN 91004685 PubMed ID: 2208618

TI Species-dependent effects of adenosine on heart rate and atrioventricular nodal conduction. Mechanism and physiological implications.

AU Froldi G; Belardinelli L

CS Department of Medicine and Pharmacology, University of Florida, College of Medicine, Gainesville 32610.

SO CIRCULATION RESEARCH, **(1990 Oct)** 67 (4) 960-78.
Journal code: DAJ; 0047103. ISSN: 0009-7330.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199011

ED Entered STN: 19910117
Last Updated on STN: 19910117
Entered Medline: 19901105

L6 ANSWER 12 OF 37 MEDLINE
AB Quantitative determination of myocardial adenosine formation and breakdown
is necessary to gain insight into the mechanism and regulation of its physiological actions. Deamination of adenosine was studied in isolated perfused rat hearts by infusion of adenosine (1 to 20 mumol X litre-1). All catabolites in the perfusates (inosine, hypoxanthine, xanthine and uric acid) were measured, as well as unchanged adenosine. Apparent uptake of adenosine was determined; it increased linearly with the concentration of adenosine infused. Adenosine was predominantly deaminated, even at low (1 mumol X litre-1) concentration. The inhibitory capacity of the adenosine deaminase inhibitor erythro-9-(2-hydroxy-3-nonyl)adenine (**EHNA**) was determined, while 5 mumol X litre-1 adenosine was infused. **EHNA** inhibited the apparent adenosine deaminase activity for 62 and 92% at 5 and 50 mumol X litre-1, respectively. When 50
mumol X litre-1 **EHNA** was infused into normoxic hearts, release of adenosine was significantly elevated, as was coronary flow. Induction of ischaemia increased total purine release four-to fivefold. Infusion of **EHNA** into ischaemic hearts did not alter total purine release, but adenosine release increased from 15 to 60% of total purines. However, when
EHNA was present, a large part of total purine release still existed of inosine, hypoxanthine, xanthiner and uric acid. This was 83% during normoxia and 40% during ischaemia. These results suggest significant contribution of IMP and GMP breakdown to purine release from isolated perfused rat hearts.
AN 86028091 MEDLINE
DN 86028091 PubMed ID: 4053134
TI Adenosine deaminase inhibition and myocardial purine release during normoxia and ischaemia.
AU Achterberg P W; Harmsen E; de Jong J W
SO CARDIOVASCULAR RESEARCH, **(1985 Oct)** 19 (10) 593-8.
Journal code: COR; 0077427. ISSN: 0008-6363.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198512
ED Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19851210

L6 ANSWER 13 OF 37 MEDLINE
AB Alteration of membrane fluidity during enzymatic methylation of membrane phosphatidyl-ethanolamine (PE) and neutralization of negative charges of membrane proteins due to methylation of carboxyl groups may contribute to sperm motility. Therefore, enzymatic phospholipid methylation and carboxymethylation, and the consequences of their inhibition on motility, were studied using human sperm. These studies gave the following results. Human sperm homoganates contained two phospholipid N-methyltransferases (PMT) which converted PE to phosphatidylcholine (PC) in the presence of S-adenosylmethionine (SAM). The first PMT converted PE to phosphatidyl-N-methylethanolamine (PME). In had a Km of 4.0 microM and a pH optimum of 8.0. The second PMT converted PME to phosphatidyl-N,N-dimethylethanolamine and PC. It had a Km of 71 microM and a pH optimum of

10.0. Spermatozoa also contained protein carboxymethylase (PCM) and methyl
aceptor protein (MAP). The intracellular levels of S-adenosylhomocysteine (SAH), an inhibitor of SAM-mediated methylations, were increased by adding
adenosine (100 microM), L-homocysteine thiolactone (L-HCT, 10 microM), and
erythro-9-(2-hydroxy-3-nonyl)-adenine (**EHNA**, 10 microM), an inhibitor of adenosine deaminase, to human sperm ejaculates that had been diluted with sodium phosphate buffer at pH 7.4 and 25 degrees. The motility index of each sperm suspension was determined every hour for 4 hr. In the presence of the mixture of adenosine, L-HCT and **EHNA**, the motility index was depressed by 57%. Under similar conditions, phospholipid methylation was depressed by 48%. Similar experiments were also conducted in the presence of 3-deazaadenosine (Deaza, 80 microM), a selective inhibitor of SAH hydrolase. In the presence of adenosine and L-HCT, Deaza depressed the motility index by 60% and phospholipid methylation by 86%. The potencies of SAH in the inhibition of phospholipid
methylation and protein carboxymethylation in sperm homogenates had the following order: PMT I greater than PCM greater than PMT II. These observations indicate that the PMT system and/or the PCM-MAP system play a
significant role in the regulation of human sperm motility.

AN 83230847 MEDLINE
DN 83230847 PubMed ID: 6860362
TI **Depression** of human sperm motility by inhibition of enzymatic methylation.
AU Sastry B V; Janson V E
NC AG-02077 (NIA)
HD-10607 (NICHD)
SO BIOCHEMICAL PHARMACOLOGY, **(1983 Apr 15)** 32 (8) 1423-32.
Journal code: 9Z4; 0101032. ISSN: 0006-2952.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198307
ED Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19830708

L6 ANSWER 14 OF 37 MEDLINE
AN 77022624 MEDLINE
DN 77022624 PubMed ID: 974331
TI The effects of three tricyclic antidepressants on arterial **eHNA** uptake and arterial responsiveness to noradrenaline (NA) [proceedings].
AU George A J
SO BRITISH JOURNAL OF PHARMACOLOGY, **(1976 Jul)** 57 (3) 432P-433P.
Journal code: B00; 7502536. ISSN: 0007-1188.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197701
ED Entered STN: 19900313
Last Updated on STN: 19900313
Entered Medline: 19770103

L6 ANSWER 15 OF 37 CAPLUS COPYRIGHT 2002 ACS

AB Methods and compns. for modulating the axonal outgrowth of central nervous system neurons are provided. Methods for stimulating the axonal outgrowth of central nervous system neurons following an injury (e.g., **stroke**, Traumatic Brain Injury, cerebral aneurism, spinal cord injury and the like) and methods for inhibiting the axonal outgrowth of central nervous system neurons in conditions such as epilepsy, e.g., post-traumatic epilepsy, and neuropathic pain syndrome, are also provided.

These methods generally involve contacting the central nervous system neurons with a purine nucleoside, or analog thereof. Preferably, inosine or guanosine is used to stimulate axonal outgrowth and 6-thioguanine is used to inhibit axonal outgrowth. The methods and compns. are particularly useful for modulating the axonal outgrowth of mammalian central nervous system neurons, such as mammalian retinal ganglion cells. Pharmaceutical and packaged formulations that include the purine nucleosides, and analogs thereof, of the invention are also provided.

AN 1999:184143 CAPLUS
DN 130:218318
TI Use of purine nucleosides for modulating the axonal outgrowth of central nervous system neurons
IN Benowitz, Larry I.
PA Children's Medical Center Corporation, USA
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9911274	A1	19990311	WO 1998-US3001	19980220	<--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
	CA 2302156	AA	19990311	CA 1998-2302156	19980220	<--
	AU 9866568	A1	19990322	AU 1998-66568	19980220	<--
	EP 1009412	A1	20000621	EP 1998-908565	19980220	
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
	JP 2001516695	T2	20011002	JP 2000-508376	19980220	
	US 2002042390	A1	20020411	US 2001-997688	20011129	
	US 2002055484	A1	20020509	US 2001-997687	20011129	
PRAI	US 1997-921902	A2	19970902			
	WO 1998-US3001	W	19980220			

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 37 CAPLUS COPYRIGHT 2002 ACS
AB Adenosine deaminase inhibitors are used for treatment of the ischemic conditions. Such conditions include thrombotic conditions, conditions characterized by ischemia and conditions characterized by inflammatory responses, including sepsis. The IC50 of 2'-deoxycoformycin in presence of of 10.mu.M adenosine was 0.63.mu.M.
AN 1994:570562 CAPLUS

DN 121:170562
TI Adenosine deaminase inhibitors for treatment of the ischemic conditions
IN Gruber, Harry Edward; Erion, Mark David; Firestein, Gary Steven; Young, Mark Alan
PA Gensia, Inc., USA
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9417809	A1	19940818	WO 1994-US1184	19940202 <--
	W: AT, AU, BB, BG, BR, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9462972	A1	19940829	AU 1994-62972	19940202 <--
PRAI	US 1993-14160		19930203		
	WO 1994-US1184		19940202		

L6 ANSWER 17 OF 37 CAPLUS COPYRIGHT 2002 ACS
AB The ability of an adenosine deaminase inhibitor erythro-9-(2-hydroxy-3-nonyl)adenine and a nucleoside transport blocker p-nitrobenzylthioinosine, via retrograde infusion delivered after normothermic ischemia in dogs, to modify reperfusion washout and preserve myocardial function was evaluated.
Functional recovery, as assessed by the mean SW/EDV (**stroke** work/end-diastolic vol.) slope, was significantly better at both reperfusion time points in the group that received cardioplegic soln. contg. inhibitors. Similar ATP degrdn. was obsd. in both groups. Total diffusible nucleosides (adenosine and inosine) accumulated during ischemia, but their washout during reperfusion was delayed in the drug-treated group.
AN 1988:622146 CAPLUS
DN 109:222146
TI Coronary sinus delivery of cardioplegic solution containing metabolic inhibitors for protection of ischemic myocardium
AU Tuchy, Gert E.; Jessen, Michael E.; Abd-Elfattah, Anwar S.; Hanan, Scott A.; Maddox, Ricky P.; Wechsler, Andrew S.
CS Med. Cent., Duke Univ., Durham, NC, USA
SO Surg. Forum (**1988**), 39, 204-7
CODEN: SUFOAX; ISSN: 0071-8041
DT Journal
LA English

L6 ANSWER 18 OF 37 USPATFULL
AB This invention provides a compound of the formula: ##STR1##

or its pharmaceutically acceptable salt thereof, wherein A is partially unsaturated or unsaturated five membered heterocyclic, or partially unsaturated or unsaturated five membered carbocyclic, wherein the 4-(sulfonyl)phenyl and the 4-substituted phenyl in the formula (I) are attached to ring atoms of Ring A, which are adjacent to each other; R.sup.1 is optionally substituted aryl or heteroaryl, with the proviso that when A is pyrazole, R.sup.1 is heteroaryl; R.sup.2 is C.sub.1-4 alkyl, halo-substituted C.sub.1-4 alkyl, C.sub.1-4 alkylamino, C.sub.1-4

dialkylamino or amino; R.sup.3, R.sup.4 and R.sup.5 are independently hydrogen, halo, C.sub.1-4 alkyl, halo-substituted C.sub.1-4 alkyl or the
like; or two of R.sup.3, R.sup.4 and R.sup.5 are taken together with atoms to which they are attached and form a 4-7 membered ring; R.sup.6 and R.sup.7 are independently hydrogen, halo, C.sub.1-4 alkyl, halo-substituted C.sub.1-4 alkyl, C.sub.1-4 alkoxy, C.sub.1-4 alkylthio,
C.sub.1-4 alkylamino or N,N-di C.sub.1-4 alkylamino; and m and n are independently 1, 2, 3 or 4. This invention also provides a pharmaceutical composition useful for the treatment of a medical condition in which prostaglandins are implicated as pathogens.

AN 2001:163224 USPATFULL
TI Sulfonylbenzene compounds as anti-inflammatory/analgesic agents
IN Ando, Kazuo, Chita-gun, Japan
Kato, Tomoki, Chita-gun, Japan
Kawai, Akiyoshi, Chita-gun, Japan
Nonomura, Tomomi, Chita-gun, Japan
PA Pfizer Inc., New York, NY, United States (U.S. corporation)
PI US 6294558 B1 20010925
WO 9711704 19970403 <--
AI US 1999-446049 19991215 (9)
WO 1999-IB970 19990531
19991215 PCT 371 date
19991215 PCT 102(e) date
DT Utility
FS GRANTED
EXNAM Primary Examiner: Raymond, Richard L.; Assistant Examiner: Patel, Sudhaker B.
LREP Richardson, Peter C., Ginsburg, Paul H., Looney, Adrian G.
CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 8683
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 19 OF 37 USPATFULL
AB The present invention provides novel human PDE8 polypeptides, polynucleotides encoding the polypeptides, expression constructs comprising the polynucleotides, host cells transformed with the expression constructs; methods for producing PDE8 polypeptides; antisense polynucleotides; and antibodies specifically immunoreactive with the PDE8 polypeptides.

AN 1999:89042 USPATFULL
TI Phosphodiesterase 8A
IN Loughney, Kate, Seattle, WA, United States
PA ICOS Corporation, Bothell, WA, United States (U.S. corporation)
PI US 5932465 19990803 <--
AI US 1997-951648 19971016 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Jacobson, Dian C.
LREP Marshall, O'Toole, Gerstein, Murray & Borun
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1846
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 20 OF 37 USPATFULL

AB Novel compounds which selectively inhibit adenosine kinase and methods of preparing adenosine kinase inhibitors are provided. Also provided are methods of treating various conditions which may be ameliorated by increased local concentrations of adenosine using adenosine kinase inhibitors.
AN 1999:13040 USPATFULL
TI Adenosine kinase inhibitors
IN Browne, Clinton E., Vista, CA, United States
Ugarkar, Bheemarao G., Escondido, CA, United States
Mullane, Kevin M., Del Mar, CA, United States
Gruber, Harry E., San Diego, CA, United States
Bullough, David A., San Diego, CA, United States
Erion, Mark D., Del Mar, CA, United States
Castellino, Angelo, San Diego, CA, United States
PA Metabasis Therapeutics, Inc., San Diego, CA, United States (U.S. corporation)
PI US 5864033 19990126 <--
AI US 1995-451236 19950526 (8)
RLI Division of Ser. No. US 1991-812916, filed on 23 Dec 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-647117, filed on 23 Jan 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-466979, filed on 18 Jan 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-408707, filed on 18 Sep 1989, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Wilson, James O.
LREP Darby & Darby
CLMN Number of Claims: 68
ECL Exemplary Claim: 1
DRWN 18 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 3491
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 21 OF 37 USPATFULL
AB Purine derivatives are provided for treatment of cellular stress, particularly hypoxia. By administering the purine derivatives by themselves or in conjunction with other compounds, particularly electron acceptor compounds and/or amino acids, the time for irreversible cellular changes, particularly mortality, can be greatly extended.
AN 1998:104730 USPATFULL
TI Method and composition for inhibiting cellular irreversible changes due to stress
IN Miller, Guy, Mountain View, CA, United States
Lou, Lillian, Palo Alto, CA, United States
Nakamura, John, San Jose, CA, United States
PA Galileo Laboratories, Inc., Sunnyvale, CA, United States (U.S. corporation)
PI US 5801159 19980901 <--
AI US 1996-607022 19960223 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Kight, John; Assistant Examiner: Crane, L. Eric
LREP Flehr Hohbach Test Albritton & Herbert LLP
CLMN Number of Claims: 20
ECL Exemplary Claim: 1,17
DRWN 14 Drawing Figure(s); 14 Drawing Page(s)

LN.CNT 717
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 22 OF 37 USPATFULL
AB This invention relates to adenosine kinase inhibitors and to nucleoside analogs, specifically to water soluble, aryl substituted 4-amino pyrrolo[2,3-d] pyrimidine and pyrazolo[3,4-d] pyrimidine nucleoside analogs having activity as adenosine kinase inhibitors The invention also relates to the preparation and use of these adenosine kinase inhibitors in the treatment of cardiovascular, and cerebrovascular diseases, inflammation and other diseases which can be regulated by increasing the local concentration of adenosine.
AN 1998:98993 USPATFULL
TI Water soluble adenosine kinase inhibitors
IN Ugarkar, Bheemarao G., Escondido, CA, United States
Erion, Mark D., Del Mar, CA, United States
Gomez Galeno, Jorge E., La Jolla, CA, United States
PA Metabasis Therapeutics, Inc., San Diego, CA, United States (U.S. corporation)
PI US 5795977 19980818 <--
AI US 1996-660532 19960607 (8)
RLI Continuation-in-part of Ser. No. US 1995-473492, filed on 7 Jun 1995 which is a continuation-in-part of Ser. No. US 1991-812916, filed on 23 Dec 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-647117, filed on 23 Jan 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-466979, filed on 18 Jan 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-408707, filed on 18 Sep 1989, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Wilson, James O.
LREP Darby & Darby P.C.
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 2977
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 23 OF 37 USPATFULL
AB The present invention provides N.sup.6 -benzyladenosine-5'-N-uronamide and related substituted compounds, particularly those containing substituents on the benzyl and/or uronamide groups, and modified xanthine ribosides, as well as pharmaceutical compositions containing such compounds. The present invention also provides a method of selectively activating an A.sub.3 adenosine receptor in a mammal, which method comprises acutely or chronically administering to a mammal in need of selective activation of its A.sub.3 adenosine receptor a therapeutically effective amount of a compound which binds with the A.sub.3 receptor so as to stimulate an A.sub.3 receptor-dependent response.
AN 1998:75569 USPATFULL
TI A3 adenosine receptor agonists
IN Jacobson, Kenneth A., Silver Spring, MD, United States
Gallo-Rodriguez, Carola, Buenos Aires, Argentina
van Galen, Philip J. M., Oss, Netherlands
von Lubitz, Dag K. J. E., Alexandria, VA, United States
Jeong, Heaok Kim, Rockville, MD, United States
PA The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
PI US 5773423 19980630 <--

AI US 1994-274628 19940713 (8)
RLI Continuation-in-part of Ser. No. US 1993-163324, filed on 6 Dec 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-91109,
filed on 13 Jul 1993, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Wilson, James O.
LREP Leydig, Voit & Mayer, Ltd.
CLMN Number of Claims: 50
ECL Exemplary Claim: 1,20
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 4850
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 24 OF 37 USPATFULL
AB This invention relates to adenosine kinase inhibitors and to nucleoside analogs, specifically to orally active, substituted 5-aryl pyrrolo[2,3-d] pyrimidine and 3-aryl pyrazolo[3,4-d] pyrimidine nucleoside analogs having activity as adenosine kinase inhibitors. The invention also relates to the preparation and use of these and other adenosine kinase inhibitors in the treatment of cardiovascular and cerebrovascular diseases, inflammation and other diseases which can be regulated by increasing the local concentration of adenosine.
AN 1998:65374 USPATFULL
TI Orally active adenosine kinase inhibitors
IN Ugarkar, Bheemarao G., Escondido, CA, United States
Erion, Mark D., Del Mar, CA, United States
Gomez Galeno, Jorge E., La Jolla, CA, United States
Castellino, Angelo J., San Diego, CA, United States
Browne, Clinton E., Gainesville, FL, United States
PA Metabasis Therapeutics, Inc., San Diego, CA, United States (U.S. corporation)
PI US 5763597 19980609 <--
AI US 1996-660506 19960607 (8)
RLI Continuation-in-part of Ser. No. US 1995-473491, filed on 7 Jun 1995 which is a continuation-in-part of Ser. No. US 1991-812916, filed on 23 Dec 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-647117, filed on 23 Jan 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-466979, filed on 18 Jan 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-408707, filed on 18 Sep 1989, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Wilson, James O.
LREP Darby & Darby
CLMN Number of Claims: 28
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2124
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 25 OF 37 USPATFULL
AB This invention relates to adenosine kinase inhibitors and to nucleoside analogs, C-4' modified pyrrolo[2,3-d]pyrimidine and pyrazolo[3,4-d]pyrimidine nucleoside analogs having activity as adenosine kinase inhibitors. The invention relates to nucleoside analogs of this kind, having zero substitutions or two substitutions at the C-4' position of the furanose (sugar) moiety. The invention also relates to the preparation and use of these adenosine kinase inhibitors in the

treatment of cardiovascular, and cerebrovascular diseases, inflammation and other diseases which can be regulated by increasing the local concentration of adenosine.

AN 1998:65373 USPATFULL
TI C-4' modified adenosine kinase inhibitors
IN Boyer, Serge H., San Diego, CA, United States
Ugarkar, Bheemarao G., Escondido, CA, United States
Erion, Mark D., Del Mar, CA, United States
PA Metabasis Therapeutics, Inc., San Diego, CA, United States (U.S. corporation)
PI US 5763596 19980609 <--
AI US 1996-660505 19960607 (8)
RLI Continuation-in-part of Ser. No. US 1995-486161, filed on 7 Jun 1995, now patented, Pat. No. US 5674998 which is a continuation-in-part of Ser. No. US 1994-191282, filed on 3 Feb 1994, now patented, Pat. No. US 5506347 And Ser. No. US 1991-812916, filed on 23 Dec 1991, now abandoned
which is a continuation-in-part of Ser. No. US 1991-647117, filed on 23 Jan 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-466979, filed on 18 Jan 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-408707, filed on 15 Sep 1989, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Wilson, James O.
LREP Darby & Darby
CLMN Number of Claims: 32
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3099
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 26 OF 37 USPATFULL
AB This invention relates to adenosine kinase inhibitors and to nucleoside analogs, specifically to water soluble, aryl substituted 4-amino pyrrolo[2,3-d] pyrimidine and pyrazolo[3,4-d] pyrimidine nucleoside analogs having activity as adenosine kinase inhibitors. The invention also relates to the preparation and use of these adenosine kinase inhibitors in the treatment of cardiovascular, and cerebrovascular diseases, inflammation and other diseases which can be regulated by increasing the local concentration of adenosine.
AN 1998:25355 USPATFULL
TI Water soluble adenosine kinase inhibitors
IN Ugarkar, Bheemarao G., Escondido, CA, United States
Erion, Mark D., Del Mar, CA, United States
Gomez Galeno, Jorge E., La Jolla, CA, United States
PA Gensia Inc., San Diego, CA, United States (U.S. corporation)
PI US 5726302 19980310 <--
AI US 1995-473492 19950607 (8)
RLI Continuation-in-part of Ser. No. US 1991-812916, filed on 23 Dec 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-647117, filed on 23 Jan 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-466979, filed on 18 Jan 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-408707, filed on 18 Sep 1989, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Wilson, James O.
LREP Darby & Darby
CLMN Number of Claims: 43

ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2082
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 27 OF 37 USPATFULL
AB This invention relates to adenosine kinase inhibitors and to nucleoside analogs, specifically to orally active, substituted 5-aryl pyrrolo[2,3-d]pyrimidine and 3-aryl pyrazolo[3,4-d] pyrimidine nucleoside analogs having activity as adenosine kinase inhibitors. The invention also relates to the preparation and use of these and other adenosine kinase inhibitors in the treatment of cardiovascular and cerebrovascular diseases, inflammation and other diseases which can be regulated by increasing the local concentration of adenosine.
AN 1998:19820 USPATFULL
TI Orally active adenosine kinase inhibitors
IN Ugarkar, Bheemarao G., Escondido, CA, United States
Erion, Mark D., Del Mar, CA, United States
Gomez Galeno, Jorge E., La Jolla, CA, United States
Castellino, Angelo J., San Diego, CA, United States
Browne, Clinton E., Gainesville, FL, United States
PA Gensia, Inc., San Diego, CA, United States (U.S. corporation)
PI US 5721356 19980224 <--
AI US 1995-473491 19950607 (8)
RLI Continuation-in-part of Ser. No. US 1991-812916, filed on 23 Dec 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-647117, filed on 23 Jan 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-466979, filed on 18 Jan 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-408707, filed on 15 Sep 1989, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Wilson, James O.
LREP Darby & Darby
CLMN Number of Claims: 57
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1667
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d 15 kwic

L6 ANSWER 15 OF 37 CAPLUS COPYRIGHT 2002 ACS
PI WO 9911274 A1 **19990311**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI WO 9911274	A1	19990311	WO 1998-US3001	19980220	<--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
CA 2302156	AA	19990311	CA 1998-2302156	19980220	<--
AU 9866568	A1	19990322	AU 1998-66568	19980220	<--
EP 1009412	A1	20000621	EP 1998-908565	19980220	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,					

IE, FI
JP 2001516695 T2 20011002 JP 2000-508376 19980220
US 2002042390 A1 20020411 US 2001-997688 20011129
US 2002055484 A1 20020509 US 2001-997687 20011129
AB . . . nervous system neurons are provided. Methods for stimulating the
axonal outgrowth of central nervous system neurons following an injury (e.g., **stroke**, Traumatic Brain Injury, cerebral aneurism, spinal cord injury and the like) and methods for inhibiting the axonal outgrowth of central. . .
IT Brain, disease
(**stroke**; purine nucleosides and analogs for modulating the axonal outgrowth of central nervous system neurons)
IT Brain, disease
(**trauma**; purine nucleosides and analogs for modulating the axonal outgrowth of central nervous system neurons)
IT 50-89-5, Thymidine, biological studies 56-65-5, 5'-ATP, biological studies 58-61-7, Adenosine, biological studies 58-63-9, Inosine 58-64-0, 5'-ADP, biological studies 58-96-8, Uridine 60-92-4, CAMP 61-19-8, Adenosine 5'-monophosphate, biological studies 65-46-3, Cytidine 68-94-0, Hypoxanthine 69-89-6, Xanthine 85-31-4, 6-Thioguanosine 118-00-3, Guanosine, biological studies 131-99-7, 5'-Inosine monophosphate 146-77-0, 2-Chloroadenosine 362-74-3, Dibutyryl cAMP 7665-99-8, CGMP 31356-94-2, 8-Bromo cyclic GMP 38048-32-7 **51350-19-7**, erythro-9-(2-Hydroxy-3-nonyl)adenine 54364-02-2 152322-58-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(purine nucleosides and analogs for modulating the axonal outgrowth of central nervous system neurons)

=> d 27 kwic

L6 ANSWER 27 OF 37 USPATFULL
PI US 5721356 19980224 <--
SUMM . . . certain conditions. For example, compounds that increase adenosine levels have been associated with the treatment of ischemic conditions such as **stroke**, as well as other conditions benefitted by enhanced adenosine levels, such as inflammation, arthritis, seizures, epilepsy and other neurological conditions.. . .
SUMM . . . reported in isolated guinea pig hearts; in these studies addition of 5'-amino-5'-deoxyadenosine to the perfusion medium, in the presence of **EHNA** to inhibit deamination, was reported to result in a 15-fold increase of adenosine release. Schrader in Regulatory Function of Adenosine;. . .
SUMM . . . an increased localized adenosine concentration is beneficial. Accordingly, the invention is directed to the treatment of ischemic conditions such as **stroke**, as well as other conditions benefitted by enhanced adenosine levels, such as inflammation, arthritis, seizures, epilepsy and other neurological conditions.. . .
DETD **Stroke** and central nervous system ("CNS") **trauma** are conditions where tissue injury results from reduced blood supply to the CNS and are thus amenable to an intervention. . . increased levels of
adenosine to the compromised tissue. It is reported that a significant component of the neurodegeneration resulting from **stroke** or

CNS **trauma** is caused by increased excitatory amino acid release and sensitivity, which results in neurons being stimulated to death. In addition. . .

=> d 28-37

L6 ANSWER 28 OF 37 USPATFULL
AN 97:120602 USPATFULL
TI 3'-deoxy or 3'-O-substituted-2',5'-oligoadenylates as antiviral agents
IN Suhadolnik, Robert J., Roslyn, PA, United States
Pfleiderer, Wolfgang, Constance, Germany, Federal Republic of
PA Temple University - Of The Commonwealth System of Higher Education, Philadelphia, PA, United States (U.S. corporation)
PI US 5700785 19971223 <--
AI US 1994-210406 19940314 (8)
RLI Continuation of Ser. No. US 1992-964111, filed on 20 Oct 1992, now abandoned which is a continuation of Ser. No. US 1990-613848, filed on 6
Dec 1990, now abandoned which is a continuation-in-part of Ser. No. US 1988-204659, filed on 9 Jun 1988, now abandoned which is a continuation-in-part of Ser. No. US 1988-144602, filed on 11 Jan 1988, now patented, Pat. No. US 4859768 which is a continuation of Ser. No. US
1984-629660, filed on 11 Jul 1984, now abandoned
DT Utility
FS Granted
LN.CNT 1294
INCL INCLM: 514/044.000
INCLS: 536/025.600; 536/025.200; 514/047.000
NCL NCLM: 514/044.000
NCLS: 514/047.000; 536/025.200; 536/025.600
IC [6]
ICM: A61K031-70
ICS: C07H021-02
EXF 514/44; 514/47; 536/25.2; 536/25.6
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 29 OF 37 USPATFULL
AN 97:107061 USPATFULL
TI A.sub.3 adenosine receptor agonists
IN Jacobson, Kenneth A., Silver Spring, MD, United States
Jeong, Heaok Kim, Rockville, MD, United States
Siddiqi, Suhaib M., Gaithersburg, MD, United States
Johnson, Carl R., Detroit, MI, United States
Secrist, III, John A., Birmingham, AL, United States
Tiwari, Kamal N., Birmingham, AL, United States
PA The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
PI US 5688774 19971118 <--
AI US 1995-396111 19950228 (8)
RLI Continuation-in-part of Ser. No. US 1994-274628, filed on 13 Jul 1994 which is a continuation-in-part of Ser. No. US 1993-163324, filed on 6 Dec 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-91109, filed on 13 Jul 1993, now abandoned
DT Utility
FS Granted
LN.CNT 2283
INCL INCLM: 514/046.000
INCLS: 514/045.000; 536/026.700; 536/027.140

NCL NCLM: 514/046.000
NCLS: 514/045.000; 536/026.700; 536/027.140
IC [6]
ICM: A61K031-70
ICS: C07H019-167; C07H019-173
EXF 514/45; 514/46; 536/26.7; 536/27.14
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 30 OF 37 USPATFULL
AN 97:91650 USPATFULL
TI C-4' modified adenosine kinase inhibitors
IN Boyer, Serge H., San Diego, CA, United States
Erion, Mark D., Del Mar, CA, United States
Ugarkar, Bheemarao G., Escondido, CA, United States
PA Gensia Inc., San Diego, CA, United States (U.S. corporation)
PI US 5674998 19971007 <--
AI US 1995-486161 19950607 (8)
RLI Continuation-in-part of Ser. No. US 1991-812916, filed on 23 Dec 1991, now abandoned And Ser. No. US 1994-191282, filed on 3 Feb 1994, now patented, Pat. No. US 5506347 , said Ser. No. US -812916 which is a continuation-in-part of Ser. No. US 1991-647117, filed on 23 Jan 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-466979, filed on 18 Jan 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-408707, filed on 18 Sep 1989, now abandoned
DT Utility
FS Granted
LN.CNT 2076
INCL INCLM: 536/027.130
INCLS: 536/027.200; 536/027.210; 536/027.230; 536/027.620; 544/254.000; 544/262.000; 544/264.000; 544/265.000; 544/266.000; 544/267.000; 544/271.000; 544/272.000; 544/273.000; 544/277.000; 544/280.000
NCL NCLM: 536/027.130
NCLS: 536/027.200; 536/027.210; 536/027.230; 536/027.620; 544/254.000; 544/262.000; 544/264.000; 544/265.000; 544/266.000; 544/267.000; 544/271.000; 544/272.000; 544/273.000; 544/277.000; 544/280.000
IC [6]
ICM: C07H019-044
ICS: C07H019-14
EXF 536/4.1; 536/27.12; 536/27.4; 536/27.62; 536/27.13; 536/27.21; 536/27.23; 544/264; 544/254; 544/262; 544/280; 544/265; 544/266; 544/267; 544/271; 544/272; 544/273; 544/277
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 31 OF 37 USPATFULL
AN 97:59186 USPATFULL
TI Methods for treating adenosine kinase related conditions
IN Firestein, Gary S., Del Mar, CA, United States
Ugarkar, Bheemarao G., Escondido, CA, United States
Miller, Leonard P., Carlsbad, CA, United States
Gruber, Harry E., Rancho Santa Fe, CA, United States
Bullough, David A., San Diego, CA, United States
Erion, Mark D., Del Mar, CA, United States
Castellino, Angelo J., San Diego, CA, United States
Browne, Clinton E., Gainesville, FL, United States
PA Gensia, Inc., San Diego, CA, United States (U.S. corporation)
PI US 5646128 19970708 <--
AI US 1994-349125 19941201 (8)
RLI Continuation of Ser. No. US 1994-192645, filed on 3 Feb 1994, now abandoned which is a continuation-in-part of Ser. No. US 1993-14190,

filed on 3 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1991-812916, filed on 23 Dec 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-647117, filed on 23 Jan 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-466979, filed on 18 Jan 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-408707, filed on 15 Sep 1989, now abandoned
DT Utility
FS Granted
LN.CNT 3276
INCL INCLM: 514/046.000
INCLS: 514/045.000; 514/825.000; 514/885.000; 514/886.000
NCL NCLM: 514/046.000
NCLS: 514/045.000; 514/825.000; 514/885.000; 514/886.000
IC [6]
ICM: A61K031-70
EXF 514/45; 514/46; 514/825; 514/885; 514/886
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 32 OF 37 USPATFULL
AN 97:40777 USPATFULL
TI Adenosine as a positive inotrop in the compromised heart
IN Dobson, Jr., James G., Shrewsbury, MA, United States
PA University of Massachusetts Medical Center, Worcester, MA, United States
(U.S. corporation)
PI US 5629298 19970513 <--
AI US 1995-402884 19950313 (8)
DT Utility
FS Granted
LN.CNT 1239
INCL INCLM: 514/045.000
INCLS: 514/046.000; 514/263.000; 536/027.600; 536/026.130
NCL NCLM: 514/045.000
NCLS: 514/046.000; 514/262.100; 514/263.340; 536/026.130; 536/027.600
IC [6]
ICM: C07H019-16
ICS: C07H019-167
EXF 514/300; 514/45; 514/46; 514/263; 536/27.6; 536/26.13
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 33 OF 37 USPATFULL
AN 96:77764 USPATFULL
TI Dual action 2',5'-oligoadenylate antiviral derivatives and uses thereof
IN Suhadolnik, Robert J., Roslyn, PA, United States
Pfleiderer, Wolfgang, Konstanz, Germany, Federal Republic of
PA Temple University-Of The Commonwealth System Of Higher Education, Philadelphia, PA, United States (U.S. corporation)
PI US 5550111 19960827 <--
AI US 1994-333930 19941103 (8)
RLI Continuation of Ser. No. US 1992-849865, filed on 12 Mar 1992, now abandoned which is a continuation-in-part of Ser. No. US 1990-613848, filed on 6 Dec 1990, now abandoned which is a continuation-in-part of Ser. No. US 1988-204649, filed on 9 Jun 1988, now abandoned which is a continuation-in-part of Ser. No. US 1988-144602, filed on 11 Jan 1988, now patented, Pat. No. US 4859768 which is a continuation of Ser. No. US
1984-629660, filed on 11 Jul 1984, now abandoned
DT Utility
FS Granted

LN.CNT 1168
INCL INCLM: 514/044.000
INCLS: 514/885.000; 514/889.000; 514/934.000; 536/025.200; 536/025.600; 536/026.400
NCL NCLM: 514/044.000
NCLS: 514/885.000; 514/889.000; 514/934.000; 536/025.200; 536/025.600; 536/026.400
IC [6]
ICM: A61K031-70
ICS: C07H021-00
EXF 536/25.2; 536/26.4; 536/25.6; 514/885; 514/889; 514/934; 514/44

L6 ANSWER 34 OF 37 USPATFULL
AN 96:12867 USPATFULL
TI Hydroxylated erythro-hydroxynonyladenines and related analogs
IN Abushanab, Elie, Peacedale, RI, United States
PA Cypros Pharmaceutical Corporation, Carlsbad, CA, United States (U.S. corporation)
PI US 5491146 19960213 <--
AI US 1994-308590 19940919 (8)
RLI Continuation-in-part of Ser. No. US 1993-4721, filed on 14 Jan 1993, now abandoned
DT Utility
FS Granted
LN.CNT 1118
INCL INCLM: 514/261.000
INCLS: 514/262.000; 514/263.000; 544/244.000; 544/263.000; 544/264.000; 544/265.000; 544/277.000
NCL NCLM: 514/263.400
NCLS: 514/151.000; 544/244.000; 544/263.000; 544/264.000; 544/265.000; 544/277.000
IC [6]
ICM: A61K031-52
ICS: C07D473-18; C07D473-32; C07D473-34
EXF 544/264; 544/277; 544/244; 544/265; 544/267; 514/261; 514/262; 514/263
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 35 OF 37 USPATFULL
AN 94:102224 USPATFULL
TI Method of treating cerebral and cardiovascular disorders employing [R]3-(2-deoxy-.beta.-D-erythro-pentofuranosyl)-3,6,7,8-tetrahydroimidazo-[4,5-d][1,3]diazepin-8-ol
IN Gallagher, Kim, Ann Arbor, MI, United States
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)
PI US 5366960 19941122 <--
AI US 1993-112746 19930826 (8)
DT Utility
FS Granted
LN.CNT 575
INCL INCLM: 514/043.000
INCLS: 514/046.000; 514/045.000; 536/027.130
NCL NCLM: 514/043.000
NCLS: 514/045.000; 514/046.000; 536/027.130
IC [5]
ICM: A61K031-70
EXF 514/45; 514/46; 514/43; 536/22.13
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 36 OF 37 USPATFULL
AN 92:59860 USPATFULL
TI Antivirals and methods for increasing the antiviral activity of AZT
IN Gruber, Harry E., San Diego, CA, United States
PA Gensia Pharmaceuticals, Inc., San Diego, CA, United States (U.S. corporation)
PI US 5132291 19920721 <--
AI US 1989-301454 19890124 (7)
DT Utility
FS Granted
LN.CNT 1103
INCL INCLM: 514/043.000
INCLS: 514/049.000; 514/050.000; 514/934.000
NCL NCLM: 514/043.000
NCLS: 514/049.000; 514/050.000; 514/934.000
IC [5]
ICM: A61K031-70
EXF 514/45-50; 514/43; 514/934
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 37 OF 37 USPATFULL
AN 91:32009 USPATFULL
TI Metabolic catheter
IN Feldman, Marc D., Charlottesville, VA, United States
Skalak, Thomas C., Charlottesville, VA, United States
Belardinelli, Luiz, Gainesville, FL, United States
PA The University of Virginia Alumni Patents Foundation, Charlottesville, VA, United States (U.S. corporation)
PI US 5009634 19910423 <--
AI US 1989-295517 19890111 (7)
DT Utility
FS Granted
LN.CNT 282
INCL INCLM: 604/027.000
INCLS: 604/035.000; 604/083.000
NCL NCLM: 604/027.000
NCLS: 604/035.000; 604/083.000
IC [5]
ICM: A61M001-00
EXF 604/27; 604/35; 604/36; 604/38; 604/43; 604/82; 604/83; 604/181; 604/182; 604/269; 604/28; 604/29; 604/44; 604/45; 604/52; 604/53; 604/56; 604/121; 604/241; 604/416; 604/902; 604/4-6; 128/207.14; 128/207.15; 128/632

=> d 31 kwic ab

L6 ANSWER 31 OF 37 USPATFULL
PI US 5646128 19970708 <--
SUMM . . . reported in isolated guinea pig hearts; in these studies addition of 5'-amino-5'-deoxyadenosine to the perfusion medium, in the presence of **EHNA** to inhibit deamination, was reported to result in a 15-fold increase of adenosine release (Schrader, in Regulatory Function of Adenosine;. . .
SUMM . . . directed to the prophylactic and affirmative treatment of ischemic conditions such as myocardial infarction, angina, percutaneous transluminal coronary angiography (PTCA), **stroke**, other thrombotic and embolic conditions, neurological conditions such as seizures and psychosis, and other conditions benefited by enhanced adenosine levels. . .

DETD . . . injury site and in other organs such as lung (ARDS) and gut, or
other edema induced by sepsis, burns or **trauma**.
AB Novel compounds which selectively inhibit adenosine kinase and methods of preparing adenosine kinase inhibitors are provided. Also provided are
methods of treating various inflammatory conditions, including arthritis
and SIRS, which may be ameliorated by increased local concentrations of adenosine using adenosine kinase inhibitors.

=> d 34 ab kwic

L6 ANSWER 34 OF 37 USPATFULL
AB This invention discloses various analogs of erythro-hydroxynonyladenine (**EHNA**) which have been modified by the addition of hydroxy groups or other moieties at the #8 or #9 carbon atoms of the side-chain portion of the molecule (i.e., the erythro-hydroxynonyl chain which is attached to the adenosine ring structure). It also discloses synthetic reagents and steps that can be used to create these and other analogs of
EHNA which contain hydroxyl, halide, acid, ester, ether, amine, azide, or other moieties at such locations, or at other controllable locations such as the #5, #6, or #7 carbon atoms on the side-chain. Analogs containing such side-chain modifications can also be modified in
the adenosine structure if desired. The hydroxylated analogs described herein have been shown to inhibit adenosine deaminase (ADA) at therapeutically useful levels. The relevant Ki values are in the range of 10.sup.-8 to 10.sup.-9, which is within a desired range of about 10.sup.-7 to about 10.sup.-10. **EHNA** analogs that have potencies within this range can effectively inhibit ADA activity on a reversible basis, without permanently poisoning the enzyme. It has also been discovered that some of these analogs have an additional therapeutic value when used to protect heart muscle against ischemic damage.
PI US 5491146 19960213 <--
AB This invention discloses various analogs of erythro-hydroxynonyladenine (**EHNA**) which have been modified by the addition of hydroxy groups or other moieties at the #8 or #9 carbon atoms. . . ring structure). It also discloses synthetic reagents and steps that can be used to create these and other analogs of **EHNA** which contain hydroxyl, halide, acid, ester, ether, amine, azide, or other moieties at
such locations, or at other controllable locations. . . are in the range of 10.sup.-8 to 10.sup.-9, which is within a desired range of about 10.sup.-7 to about 10.sup.-10. **EHNA** analogs that have potencies within this range can effectively inhibit ADA activity on a reversible basis, without permanently poisoning the. . .
SUMM The compound erythro-hydroxynonyladenine (**EHNA**, which is usually pronounced as "eenah") is known to inhibit the activity of an enzyme called adenosine deaminase (ADA, also. . .
SUMM **EHNA**, a relatively mild ADA inhibitor, is a stereoisomer with the following chemical structure, which shows the numbering of the carbon. . .
SUMM . . . often referred to as "threo-" compounds. A racemic mixture (i.e., a mixture containing both D (+) and L isomers) containing **EHNA** was identified as an ADA inhibitor in Schaeffer and Schwender 1974. Subsequent reports, including Bastian et al 1981 and

Baker. . .

SUMM Various analogs and derivatives of **EHNA** have been described in reports such as Harriman et al 1992. Those other analogs are not related to the **EHNA** analogs described herein.

SUMM **EHNA** apparently is metabolized and cleared from the mammalian bloodstream fairly rapidly (McConnell et al 1980; Lambe and Nelson 1982). In addition, ADA inhibition by **EHNA** is not as strong as certain other known compounds, including deoxycoformycin (dCF, also known as Pentostatin). The Ki value of. . . 1989), it was found to cause serious and unpredictable toxic side effects in some animals. Therefore, attention has returned to **EHNA** as a milder or "softer" ADA inhibitor with fewer side effects. The Ki value of **EHNA** is about 4.times.10.sup.-9, which indicates that **EHNA** binds to ADA about a thousand times less tightly than dCF.

SUMM One object of this invention is to disclose a class of hydroxylated derivatives of **EHNA** which can inhibit ADA activity at therapeutically effective levels without irreversibly inactivating (poisoning) the ADA enzyme.

SUMM Another object of this invention is to disclose synthetic reagents and methods that can be used to create analogs of **EHNA** which contain hydroxyl, halide, acid, ester, ether, amine, azide, or other moieties at various controllable locations in the side chain.

SUMM Another object of this invention is to disclose a new set of **EHNA** analogs which can be used to slow down the degradation of certain types of useful therapeutic drugs by ADA.

SUMM This invention discloses various analogs of erythro-hydroxynonyladenine (**EHNA**) which have been modified by the addition of hydroxy groups or other moieties at the #8 or #9 carbon atoms. . . ring structure). It also discloses synthetic reagents and steps that can be used to create these and other analogs of **EHNA** which contain hydroxyl, halide, acid, ester, ether, amine, azide, or other moieties at such locations, or at other controllable locations. . . are in the range of 10.sup.-8 to 10.sup.-9, which is within a desired range of about 10.sup.-7 to about 10.sup.-10. **EHNA** analogs that have potencies within this range can effectively inhibit ADA activity on a reversible basis, without permanently poisoning the. . .

DRWD FIG. 1 depicts a series of chemical reactions used to create 9'-hydroxy(+)-**EHNA**, designated as Compound [10].

DRWD FIG. 2 depicts the reactions used to create 8'-hydroxy(+)-**EHNA**, designated as Compound [23].

DRWD FIG. 3 depicts the reactions used to create 8', 9'-dihydroxy(+)-**EHNA**, designated as Compound [14].

DRWD FIG. 4 depicts the reactions used to create other analogs of **EHNA** which have been modified by the addition of various non-hydroxy moieties at the #9 carbon atom.

DETD This invention describes analogs of **EHNA** in which the side chain (i.e., theerythro-hydroxynonyl portion, which is attached to an adenyl structure) hasbeen chemically modified by addition of a hydroxyl or other group. Useful analogs within this class include **EHNA** analogs that are pharmacologically acceptable inhibitors of adenosine deaminase, as discussed below.

DETD This invention also discloses a method of synthesizing analogs of **EHNA** in which a hydroxyl or other moiety has been added to the side chain. This method comprises the following steps:

DETD Example 1, below, sets forth in detail the reagents and reactions used to synthesize a number of hydroxylated or halogenated **EHNA** analogs. The epoxide starting reagent, intermediate compounds generated during the multi-step synthesis, and the final **EHNA** analogs

are identified by the full chemical names in the subheadings under Example 1, and by bracketed numbers that are. . .

DETD One of the hydroxylated **EHNA** analogs which was shown to inhibit ADA activity is Compound [10]. Its full chemical name is 9-[2(S),9-dihydroxy-3(R)-nonyl]adenine, and it is also referred to herein as 9-hydroxy-**EHNA**, or as 9-OH-**EHNA**. Its synthesis is depicted in FIG. 1.

DETD Another hydroxylated **EHNA** analog which inhibits ADA activity is Compound [23]. Its full chemical name is 9-[2(S),8-dihydroxy-3(R)-nonyl]adenine; itis also referred to as 8-hydroxy-**EHNA**, or as 8-OH-**EHNA**. Its synthesis is depicted in FIG. 2.

DETD Compound [14] is a dihydroxylated **EHNA** analog with hydroxy groups added to both the 8' and 9' carbon atoms. Its synthesis is depicted in FIG. 3.. . .

DETD . . . al 1984 and 1988. It controls the orientation of the substituents on the two chiral carbon atoms in the final **EHNA** analog, which are provided by the #3 and #4 carbons in the epoxide. To synthesize different stereoisomers of any of the **EHNA** analogs discussed herein, different epoxide stereoisomers having any desired chiral configuration can be used as the starting reagent.

DETD . . . served as a protective group for the oxygen atom. In the final step of synthesis of each of the hydroxylated **EHNA** analogs, the benzyl group was displaced by hydrogen to create a hydroxyl group on the #2 carbon of the side chain. That #2 hydroxyl group is part of the normal **EHNA** molecule. If desired, that hydroxyl group can be eliminated by using a starting epoxide without a protected oxygen atom, or. . . azide, or other group, as described above. If a moiety is desired at the #1 carbon atom in the final **EHNA** analog, it can be provided by using a starting epoxide having the desired moiety or a precursor at the #4. . .

DETD . . . #1 and #2 carbon atoms in 1-pentenylmagnesium bromide; those carbon atoms ultimatelybecome the #8 and #9 carbon atoms in the **EHNA** analogs of this invention. The unsaturated carbon atoms in the double-bonded pentenyl compound becomeattachment points for hydroxyl groups during the. . .

DETD Using either of these approaches, the location of the hydroxyl group on theside chain of an **EHNA** analog can be controlled by using a pentenylmagnesiumbromide (or similar) compound having a double bond in any desired location.A 2-pentenyl. . . a double bond between its #2 and #3 carbonatoms, which become the #8 and #7 carbon atoms in the final **EHNA** analog. A 3-pentenyl reagent (having a double bond between its #3 and #4 carbon atoms) would generate hydroxyl groups attached to the #7 or #6 carbons in the **EHNA** analog.

DETD The method used to create the adenyl structure in the **EHNA** analogs described herein offers a general method for making various changes in theadenine group. The adenyl structure was provided by. . .

DETD If desired, alternate heterocyclic reagents could be used instead of ADCP, to create analogs of **EHNA** with modified adenine structures, either as moieties attached to one of the rings, or as differing atoms incorporated into either of the rings. Cristalli et al 1988 and 1991 report that certain analogues of **EHNA** with modified adenine structures (such as a 3-deaza-**EHNA** derivative) are active as ADA inhibitors. Such modifications to the adenyl structure could be incorporated into the analogs of this. . .

DETD All the hydroxylated **EHNA** analogs which were tested for ADA

inhibition (as described in Example 2) were shown to be active. The 9-hydroxy analog (compound [10]) was the strongest binding agent of the three, with a Ki value of 3.4.times.10.sup.-9 ; the 8-hydroxy-**EHNA** analog (compound [23]) was the weakest, with a Ki value of 11.times.10.sup.-9. The 8,9-dihydroxy analog (compound 14]) had an intermediate. . .

DETD The **EHNA** analogs described herein can be administered as adjuncts to prolong the half-lives and increase the effectiveness of chemotherapeutic drugs (usually. . .

DETD In addition, the hydroxylated **EHNA** analogs described herein were tested forprotection against tissue damage caused by ischemia (lack of adequate bloodflow, which occurs during various events such as heart attack, cardiac arrest, and **stroke**). In tests involving hearts removed from lab animals, 9-OH-**EHNA** provided a significantly higher level of protection against an important form of muscle damage, compared to unmodified **EHNA**. These results and the test procedures are described in Example 5. This useful biological activity could not have been predicted. . . prior to the experiments, and it helps overcome any presumption of obviousness of hydroxylated analogs based upon prior art concerning **EHNA**.

DETD . . . render the analog pharmacologically unacceptable. By way of example, the hydroxylated compounds [10], [14], and [23] are all analogs of **EHNA**; by contrast, the standard form of **EHNA** is not regarded as an analog of 9-hydroxy-**EHNA**. Any coverage of claims which refer to additional analogs derived from the hydroxylated analogs disclosed herein is limited to analogs. . .

DETD . . . al 1984 and 1988. This epoxide determines the orientation of the substituentsòn the two chiral carbon atoms in the final **EHNA** analog, which are providedby the #3 and #4 carbons in the epoxide. To synthesize different stereoisomers of any of the **EHNA** analogs discussed herein, different epoxide stereoisomers having any desired chiral configuration can be used as the starting reagent. A benzyl. . .

DETD This compound is the 9-hydroxy analog of **EHNA** which was tested as describedin Example 2 and shown to be an effective inhibitor of ADA activity.

DETD This compound is the 8,9-dihydroxy analog of **EHNA** which was tested as described in Example 2 and shown to be an effective inhibitor of ADA activity.

DETD This compound is the 8-dihydroxy analog of **EHNA** which was tested as described in Example 2 and shown to inhibit ADA activity.

DETD Synthesis of Various Other Analogs of **EHNA**

DETD This example and FIG. 4 depict the synthesis of several additional analogs of **EHNA**. Except as noted, the synthetic reactions described below used thebenzyl-protected compound [9] (described in Example 1) as the starting reagent.. . .

DETD Testing of 9-OH-**EHNA** for Protection Against Ischemic Damage to Tissue

DETD After synthesis of the 9-hydroxy and 8-hydroxy analogs of **EHNA** , samples were provided by the Applicant to Dr. Robert Rodgers of the Department of Pharmacology and Toxicology at the University of Rhode Island. There were sufficient quantities of 9-hydroxy-**EHNA** for thorough testing as described below, while quantities of 8-hydroxy-**EHNA** were very small. Accordingly, most tests used 9-hydroxy-**EHNA** and compared it to unmodified **EHNA** and to disulfiram, an unrelated compound that is known to have certain protectiveanti-ischemic effects in cardiovascular tissue.

DETD . . . hearts were allowed to stabilize for 10minutes, then they were

treated for 10 minutes with one of the test drugs (**EHNA**, 9-hydroxy-**EHNA**, or disulfiram) or buffered saline containing eitherdilute ethyl alcohol (used to increase the solubility of **EHNA** or 9-hydroxy-**EHNA**) or dilute dimethyl sulfoxide (used to increase solubility of disulfiram). Following stabilization and treatment, the hearts were subjected to simulated. . .

DETD The results indicated that both **EHNA** and 9-hydroxy-**EHNA** reduced the incidence of fibrillation, as shown in Table 1

DETD TABLE 1

	Total #	# fibrillating	% fibr.
Controls	13	4	31
EHNA	7	1	14
9-OH--**EHNA**	9	1	11
Disulfiram	5	2	40

DETD Both **EHNA** and 9-OH-**EHNA** caused a moderate increase in both LVPP and in coronary flow rate after ischemia.

DETD The most important difference observed between **EHNA** and 9-OH-**EHNA** appeared in measurements of LVEDP (left ventricular end diastolic pressure). This parameter indicates whether the muscles of the left ventricular. . . longer has sufficient flexibility and elasticity to properly fill the chambers with blood during diastole. In the tests carried out, 9-OH-**EHNA** provided a significantly higher level of protectionagainst muscle stiffening than unmodified **EHNA**.

DETD . . . prior to the experiments, and it helps overcome any presumption of obviousness of hydroxylated analogs based upon prior art concerning **EHNA**.

DETD Thus, there has been shown and described a new class of **EHNA** analogs havingmodified side chains, which are useful in inhibiting ADA activity; also disclosed herein are methods of synthesizing such analogs,. . .

=> d 35 ab kwic

L6 ANSWER 35 OF 37 USPATFULL

AB The present invention discloses the use of [R]-3-(2-deoxy-.beta.-D-erythropentofuranosyl)-3,6,7,8-tetrahydroimidazo-[4,5-d][1,3]diazepin-8-ol, also commonly known as pentostatin, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprised of such compounds, in the prophylactic or affirmative treatment of cerebral and cardiovascular disorders such as cerebral and myocardial ischemia. The invention also discloses the administration of pentostatin along with adenosine in the prophylactic or affirmative treatment of cerebral and cardiovascular disorders.

PI US 5366960 19941122 <--

SUMM . . . the United States. The frequency of the most debilitating problems (such as myocardial infarction, postoperative low cardiac output syndrome, and **stroke**) are estimated to be in the range of 5-10%, whereas modest cardiac dysfunction and cognitive disorders may

have frequencies of. . .

SUMM . . . in CABG procedures, but ischemia remains a significant and serious risk that can lead to myocardial infarction, prolonged postoperative dysfunction, **stroke**, or cognitive disorders.

SUMM . . . used to enhance or maintain local adenosine levels in the heart and brain. For example, pentostatin and erythro-9 (2-hydroxy-3-nonyl) adenine (**EHNA**) improved functional and metabolic recovery after global ischemia in isolated rabbit (Bolling SF, Bies LE, Bore El, Gallagher KP, Augmenting. . . hypoxemic rat cerebral cortex. J Cereb Blood Flow Metab 8: 733-741, 1988; Phillis JW, O'Regan MH: Deoxycoformycin antagonizes ischemia-induced neuronal **degeneration**. Brain Res Bull 22: 537- 540, 1989; Phillis JW, Walter GA, Simpson RE: Brain adenosine and transmitter amino acid release. . .

SUMM The invention also includes a method of treating cerebral ischemia, cerebral infarction, cerebral vasospasm, cardiac arrest, cerebral **trauma**, myocardial ischemia, myocardial infarction, peri-, intra-, and post-operative cardiac and cerebral ischemic events comprising prophylactically or affirmatively administering to a. . .

SUMM The invention also includes a method of treating **stroke** or other event involving an undesired, restricted or decreased blood flow, such as atherosclerosis, in patients in need thereof which. . .

DETD The term, "cerebral and cardiovascular disorders" is defined herein to mean cerebral ischemia, cerebral infarction, cerebral vasospasm, cardiac arrest, cerebral **trauma**, myocardial ischemia, myocardial infarction, peri-, intra-, and post-operative cardiac and cerebral ischemic events. The term ischemic events may be defined to include **stroke** or other events involving an undesired, restricted or decreased blood flow, such as atherosclerosis.

DETD . . . to define left ventricular function (utilizing arrays of sonomicrometers and high fidelity pressure transducers to enable calculation of preload recruitable **stroke** work), aortic crossclamping for a total of 90 minutes (30 minutes of normothermic, global ischemia followed by blood cardioplegia and. . .

DETD As shown in FIG. 3, postischemic left ventricular performance (preload recruitable **stroke** work) was restored to baseline levels or greater in the pentostatin (0.2 mg/kg; approximate human equivalent dose 4.0 mg/m.sup.2) pretreatment. . .

=>

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=> file embase biosis medline caplus uspatfull
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

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FILE 'MEDLINE' ENTERED AT 18:46:37 ON 14 MAY 2002

FILE 'CAPLUS' ENTERED AT 18:46:37 ON 14 MAY 2002
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FILE 'USPATFULL' ENTERED AT 18:46:37 ON 14 MAY 2002
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=> s PDE2 inhibitor or phosphodiesterase 2 inhibitor or PDE2 antagonist
L1          35 PDE2 INHIBITOR OR PHOSPHODIESTERASE 2 INHIBITOR OR PDE2
ANTAGONI
               ST

=> s perception or learning or concentration or dementia or alzheimer's or
depression or parkinson's
   3 FILES SEARCHED...
L2     5972197 PERCEPTION OR LEARNING OR CONCENTRATION OR DEMENTIA OR
ALZHEIMER
               'S OR DEPRESSION OR PARKINSON'S

=> s l1 and l2
L3          14 L1 AND L2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4            7 DUP REM L3 (7 DUPLICATES REMOVED)

=> d l4 1-7 ab bib kwic

L4   ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2002 ACS
AB   The invention discloses the use of selective phosphodiesterase
     2 inhibitors for producing medicaments to improve
     cognition, powers of concn., learning capability,
     and/or memory retention.
AN   2002:107116  CAPLUS
DN   136:145267
TI   Selective phosphodiesterase 2 inhibitors
     used as medicaments for improving cognition
IN   Boss, Frank-Gerhard; Hendrix, Martin; Konig, Gerhard; Niewohner, Ulrich;
     Schlemmer, Karl-Heinz; Schreiber, Rudy; Van Der Staay, Franz-Josef;
     Schauss, Dagmar
PA   Bayer Aktiengesellschaft, Germany
SO   PCT Int. Appl., 18 pp.
     CODEN: PIXXD2
DT   Patent
LA   German
FAN.CNT 1
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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002009713	A2	20020207	WO 2001-EP8609	20010719
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	DE 10122893	A1	20020321	DE 2001-10122893	20010511
PRAI	DE 2000-10037411	A	20000801		
	DE 2001-10122893	A	20010511		

OS MARPAT 136:145267

TI Selective **phosphodiesterase 2 inhibitors** used as medicaments for improving cognition

AB The invention discloses the use of selective **phosphodiesterase 2 inhibitors** for producing medicaments to improve cognition, powers of **concn.**, **learning** capability, and/or memory retention.

ST **phosphodiesterase 2 inhibitor** cognition memory **learning concn**

IT Memory, biological
(and **concn.** power; selective **phosphodiesterase 2 inhibitors** for improving cognition)

IT Mental disorder
(**dementia**; selective **phosphodiesterase 2 inhibitors** for improving cognition)

IT Mental disorder
(depression; selective **phosphodiesterase 2 inhibitors** for improving cognition)

IT Brain
(frontal lobe, degeneration; selective **phosphodiesterase 2 inhibitors** for improving cognition)

IT Anti-Alzheimer's agents
Antiparkinsonian agents
Cognition enhancers
Human
Learning
(selective **phosphodiesterase 2 inhibitors** for improving cognition)

IT Brain, disease
(stroke; selective **phosphodiesterase 2 inhibitors** for improving cognition)

IT Brain, disease
(trauma; selective **phosphodiesterase 2 inhibitors** for improving cognition)

IT 9036-21-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IV; selective **phosphodiesterase 2 inhibitors** for improving cognition)

IT 9040-59-9, Phosphodiesterase II
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; selective **phosphodiesterase 2 inhibitors** for improving cognition)

IT 7665-99-8, Cyclic GMP 9068-52-4, Phosphodiesterase V
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(selective **phosphodiesterase 2 inhibitors**

for improving cognition)
IT 213324-52-8
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective **phosphodiesterase 2 inhibitors**
for improving cognition)

L4 ANSWER 2 OF 7 USPATFULL
AB This invention provides pharmaceutical compositions containing compounds
for the treatment of neoplasia in mammals. The increase in PKG activity of a compound is determined along with COX inhibitory activity. Growth inhibitory and apoptosis inducing effects on cultured tumor cells are also determined. Compounds that exhibit increase PKG activity, growth inhibition and apoptosis induction, but preferably not substantial prostaglandin inhibitory activity, are desirable for the treatment of neoplasia.
AN 2002:16884 USPATFULL
TI METHODS FOR IDENTIFYING COMPOUNDS FOR INHIBITION OF NEOPLASTIC LESIONS, AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS
IN THOMPSON, W. JOSEPH, DOYLESTOWN, PA, UNITED STATES
LIU, LI, AMBLER, PA, UNITED STATES
LI, HAN, YARDLEY, PA, UNITED STATES
PI US 2002009764 A1 20020124
AI US 1999-414628 A1 19991008 (9)
DT Utility
FS APPLICATION
LREP ROBERT W STEVENSON, CELL PATHWAYS INC, 702 ELECTRONIC DR, HORSHAM, PA, 10944
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 25 Drawing Page(s)
LN.CNT 2468
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DRWD . . . obtained from HTB-26 neoplastic cells, as assayed from the eluent from a DEAE-Trisacryl M column with low and high substrate **concentration**.
DRWD . . . obtained from LnCAP neoplastic cells, as assayed from the eluent from a DEAE-Trisacryl M column with low and high substrate **concentration**.
DETD . . . which are graphically presented in FIG. 2. One observation about peak B illustrated in FIG. 2 is that increasing substrate **concentration** of cGMP dramatically enhanced activity when contrasted to peak A. While this observation is consistent with its being a PDE2,. . .
DETD . . . assayed with 2 .mu.M cAMP substrate and showed a two-fold activation by 5 .mu.M cGMP (see Figure -Y). The selective **PDE2 inhibitor** EHNA inhibited 2 .mu.M cGMP PDE activity in this Peak B with an IC.sub.50 of 1.6 .mu.M and inhibited 2.0. . .
DETD . . . For example, in Eadie-Hofstee plots of Peak A, cyclic GMP hydrolysis shows single line with negative slope with increasing substrate **concentrations**, indicative of Michaelis-Menten kinetic behavior. Peak B, however, shows the novel property for cGMP hydrolysis in the absence of cAMP. . .
DETD . . . positive-cooperative kinetic behavior in the presence of cGMP substrate, was the increased cGMP hydrolytic activity in the presence of
increasing **concentrations** of cGMP substrate. This was discovered by comparing 0.25 .mu.M, 2 .mu.M and 5 .mu.M **concentrations** of cGMP in the presence of PDE peak B after a

second DEAE separation to rule out cAMP hydrolysis and to rule out this new enzyme being a previously identified PDE5. Higher cGMP **concentrations** evoked disproportionately greater cGMP hydrolysis with PDE peak B, as shown in FIG. 2.

DETD [0077] Different PDE inhibitors were studied using twelve **concentrations** of drug from 0.01 to 100 .mu.M and substrate **concentration** of 0.25 .mu.M .sup.3H-cGMP. IC.sub.50 values were calculated with variable slope, sigmoidal curve fits using Prism 2.01 (GraphPad). The results. . .

DETD . . . A and the novel peak B (Section IA) were observed in their respective cGMP-hydrolytic activities in the presence of varying **concentrations** of cGMP-dependent protein kinase G (which phosphorylates typical PDE5). Specifically, peak A and peak B fractions from Section IA were incubated with different **concentrations** of protein kinase G at 30.degree. C. for 30 minutes. Cyclic GMP hydrolysis of both peaks has assayed after phosphorylation. . .

DETD . . . cells are exposed to 1.3% DMSO for 9 days and then washed and resuspended in Dulbecco's phosphate-buffered saline at a **concentration** of 3.times.10.sup.6 cells/mL.

DETD . . . (3.times.10.sup.6 cells/mL) are incubated for 15 minutes at 37.degree. C. in the presence of the compounds tested at the desired **concentration**. Cells are then stimulated by A23187 (5.times.10.sup.-6 M) for 15 minutes. PGE.sub.2 secreted into the external medium is measured as. . .

DETD . . . presence and absence of the test compound. Residual (i.e., less than about 25%) or no COX inhibitory activity at a **concentration** of about 100 .mu.M is indicative that the compound should be evaluated further for usefulness for treating neoplasia.

DETD . . . a combined cGMP hydrolytic activity is assayed simultaneously. The test compound is then incubated with the cell culture at a **concentration** of compound between about 200 .mu.M to about 200 .mu.M. About 24 to 48 hours thereafter, the culture media is. . .

DETD . . . useful for treating neoplasia. Significant inhibitory activity greater than that of the benchmark, exisulind, preferably greater than 50% at a **concentration** of 10 .mu.M or below, is indicative that a compound should be further evaluated for antineoplastic properties. Preferably, the IC.sub.50. . .

DETD . . . replicates. After six days in culture, the cells are fixed by the addition of cold trichloroacetic acid to a final **concentration** of 10% and protein levels are measured using the sulforhodamine B (SRB) colorimetric protein stain assay as previously described by. . .

DETD . . . useful for treating neoplastic lesions. Preferably, an IC.sub.50 value is determined and used for comparative purposes. This value is the **concentration** of drug needed to inhibit tumor cell growth by 50% relative to the control. Preferably, the IC.sub.50 value should be. . .

DETD . . . of cells with test compounds involves either pre- or post-confluent cultures and treatment for two to seven days at various **concentrations**. Apoptotic cells are measured in both the attached and "floating" compartments of the cultures. Both compartments are collected by removing. . .

DETD [0133] Fold stimulation (FS=OD.sub.max/OD.sub.veh), an indicator of apoptotic response, is determined for each compound tested at a given **concentration**. EC.sub.50 values may also be determined by evaluating a series of **concentrations** of the test compound.

DETD [0134] Statistically significant increases in apoptosis (i.e., greater than 2 fold stimulation at a **concentration** of 100 .mu.M) are further indicative that the compound is useful for treating neoplastic

lesions. Preferably, the EC.sub.50 value for. . . for the compound to be further considered for potential use for treating neoplastic lesions.

EC.sub.50 is herein defined as the **concentration** that causes 50% induction of apoptosis relative to vehicle treatment.

DETD . . . COX inhibitory activity in accordance with the protocol for the COX assay, supra. FIG. 4 shows the effect of various **concentrations** of either sulindac sulfide or exisulind on purified cyclooxygenase (Type 1) activity. Cyclooxygenase activity was determined using purified cyclooxygenase from. . .

DETD . . . PDE inhibitory activity in accordance with the protocol for the assay described supra. FIG. 6 shows the effect of various **concentrations** of sulindac sulfide and exisulind on either PDE4 or cGMP PDE activity purified from human colon HT-29 cultured tumor cells,. . .

DETD [0162] FIG. 12 shows the apoptosis inducing properties of compound E. HT-29 colon adenocarcinoma cells were treated with the indicated **concentration** of compound E for 48 hours and apoptosis was determined by the DNA fragmentation assay. The calculated EC.sub.50 value was. . .

DETD [0163] FIG. 13 shows the apoptosis inducing properties of compound B. HT-29 colon adenocarcinoma cells were treated with the indicated **concentration** of compound B for 48 hours and apoptosis was determined by the DNA fragmentation assay. The calculated EC.sub.50 value was. . .

DETD . . . PDE5 inhibitory activity in accordance with the protocol for the assay supra. FIG. 14 shows the inhibitory effect of various **concentrations** of sulindac sulfide and exisulind on the growth of HT-29 cells. HT-29 cells were treated for six days with various. . .

DETD . . . FIG. 16 shows the growth inhibitory activity of test compound E. HT-29 colon adenocarcinoma cells were treated with the indicated **concentration** of compound E for six days and cell number was determined by the SRB assay. The calculated IC.sub.50 value was. . .

DETD . . . had to be normalized to the highest dose exisulind sample). Thus, after the protein assays are performed, the total protein **concentration** of the various samples must be normalized (e.g., by dilution).

DETD [0203] For each drug **concentration** and control, two PKG assays are performed, one with added cGMP, and one without added cGMP, as described in detail. . .

DETD . . . transferred to fresh microcentrifuge tubes immediately after spinning. BioRad DC Protein Assay (Temecula, Calif.) is performed to determine the protein **concentrations** in samples. The samples are normalized for protein **concentration**, as described above.

DETD [0215] A goat-anti-PKG primary antibody is diluted to the recommended **concentration**/dilution in fresh TBST/5% nonfat dry milk. The nitrocellulose membrane is placed in the primary antibody solution and incubated one hour. . .

DETD . . . 15 .mu.M. In addition, the percent apoptosis for Compound I in SW-480 is shown in Table 12 at various drug **concentrations**.

TABLE 12

Apoptosis Induction of HT-29 Cells of SW-480
Colon Adenocarcinoma Cells by Compound I

as Determined by Morphology
Treatment Dose % Apoptosis

. . .
DETD . . . 96-well plates at a density of 1000 cells per well. Twenty-four hours after plating, the cells were dosed with various **concentrations** of the free base of Compound I solubilized in DMSO (final **concentration** 0.1%). The effect of the drug on tumor cell growth was determined using the neutral red cytotoxicity assay following five. . .
DETD . . . growth inhibitory effects regardless of the histogenesis of the tumor from which the cell lines were derived. The GI.sub.50 value (**concentration** of drug to inhibit growth by 50% relative to vehicle control) calculated for all cell lines was 1-2 .mu.M.
DETD . . . AMP, cUMP, cCMP, 8-bromo-cAMP, 2'-O-butyl-cAMP and 2'-O-butyl-cGMP did not compete with cGMP in binding. Cyclic IMP and 8-bromo-cGMP at high **concentration** (100 .mu.M) can partially compete with cGMP (2 .mu.M) binding. None of the PDE5 inhibitors showed any competition with cGMP. . .

L4 ANSWER 3 OF 7 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB PURPOSE: Pharmacologic treatments are gaining widespread acceptance as first-line therapy for anal fissure. However, existing treatments have limited clinical usefulness because of side effects and incomplete healing rates. METHODS: Fresh human surgical resection specimens containing internal anal sphincter and rectal circular muscle were collected. Strips of smooth muscle were cut from each muscle group and mounted in a superfusion organ bath. The effects of increasing **concentrations** of phosphodiesterase inhibitors were evaluated. RESULTS: All phosphodiesterase inhibitors tested caused a dose-dependent reduction in the tone of the internal anal sphincter, with potencies as follows: vinpocentine (phosphodiesterase-1 inhibitor; 50 percent maximum inhibition **concentration** = 0.87 .+-. 0.10 .mu.M), erythro-9-(2-hydroxy-3-nonyl) adenine hydrochloride (**phosphodiesterase-2 inhibitor**; 32 .+-. 4.8 .mu.M), trequinsin (phosphodiesterase-3 inhibitor; 0.28 .+-. 0.041 .mu.M), rolipram (phosphodiesterase-4 inhibitor; 63 .+-. 9 .mu.M), zaprinast (phosphodiesterase-1,5,6,9,11 inhibitor; 3 .+-. 0.69 .mu.M), and dipyridamole (phosphodiesterase-5,6,8,10,11 inhibitor; 5.5 .+-. 2 .mu.M). Although all inhibitors were also effective on rectal circular muscle strips, erythro-9-(2-hydroxy-3-nonyl) adenine hydrochloride, trequinsin, and rolipram were at least an order of magnitude more potent in this tissue than in the internal anal sphincter. CONCLUSIONS: There are several functionally important phosphodiesterases in the internal anal sphincter and rectal circular muscle. Both adenosine 3',5'-cyclic monophosphate and guanosine 3',5'-cyclic monophosphate appear to be important in the myogenic tone of the internal anal sphincter, and this study provides further evidence of the sphincteric specialization of this tissue. Phosphodiesterase inhibitors might represent a new therapy for the treatment of anal fissure.
AN 2002145604 EMBASE
TI Phosphodiesterase inhibitors cause relaxation of the internal anal sphincter in vitro.
AU Jones O.M.; Brading A.F.; Mortensen N.J.McC.
CS O.M. Jones, Department of Pharmacology, Mansfield Road, Oxford OX1 3QT, United Kingdom

SO Diseases of the Colon and Rectum, (2002) 45/4 (530-536).
Refs: 33
ISSN: 0012-3706 CODEN: DICRAG
CY United States
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
AB . . . of smooth muscle were cut from each muscle group and mounted in a
superfusion organ bath. The effects of increasing **concentrations** of phosphodiesterase inhibitors were evaluated. RESULTS: All phosphodiesterase inhibitors tested caused a dose-dependent reduction in the tone of the internal anal sphincter, with potencies as follows: vinpocentine (phosphodiesterase-1 inhibitor; 50 percent maximum inhibition
concentration = 0.87 .+-. 0.10 .mu.M), erythro-9-(2-hydroxy-3-nonyl) adenine hydrochloride (**phosphodiesterase-2 inhibitor**; 32 .+-. 4.8 .mu.M), trequinsin (phosphodiesterase-3 inhibitor; 0.28 .+-. 0.041 .mu.M), rolipram (phosphodiesterase-4 inhibitor; 63 .+-. 9 .mu.M), zaprinast (phosphodiesterase-1,5,6,9,11. . .
CT Medical Descriptors:
*anus sphincter
*muscle relaxation
anus fissure: ET, etiology
concentration response
drug potency
enzyme specificity
muscle tone
IC 50
drug effect
human
male
female
clinical article
human tissue
aged
adult
article
*phosphodiesterase inhibitor: PD, pharmacology
vinpocentine: CB, drug combination
vinpocentine: CM, drug comparison
vinpocentine: PD, pharmacology
erythro. . .

L4 ANSWER 4 OF 7 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AB 1. Type 4 phosphodiesterase (PDE4) inhibitors mimic the pharmacological actions of alpha2-adrenoceptor antagonists. This has been postulated as the mechanism by which PDE4 inhibitors induce emesis and was also demonstrated by their ability to reverse xylazine/ketamine-induced anaesthesia. We further characterized this latter effect since it appears to reflect the emetic potential of PDE4 inhibitors. 2. Selective inhibitors of PDE 1, 2, 3, 4 and 5 were studied in rats, on the duration of anaesthesia induced by the combination of xylazine (10 mg kg(-1), i.m.)
and ketamine (10 mg kg(-1), i.m.). PMNPQ (i.e. 6-(4-pyridylmethyl)-8-(3-nitrophenyl)quinoline) - PDE4 inhibitor: 0.01-3 mg kg(-1)), like MK-912

(alpha(2)-adrenoceptor antagonist: 0.01-3 mg kg(-1)), dose-dependently reduced the duration of anaesthesia. In contrast, vinpocetine (PDE1 inhibitor), EHNA (**PDE2 inhibitor**), milrinone (PDE3 inhibitor) and zaprinast (PDE5 inhibitor) had no significant effect at the doses tested (1-10 mg kg(-1)). Analysis of plasma and cerebrospinal fluid (CSF) of treated animals confirmed the absorption and distribution to the brain of the inactive inhibitors. 3. Neither MK-912 (3 mg kg(-1)) nor PMNPQ (0.1- 1 mg kg(-1)) altered the duration of anaesthesia induced via a non-alpha(2)-adrenoceptor pathway (sodium pentobarbitone 50 mg kg(-1), i.p.). 4. Central NK(1) receptors are involved in PDE4 inhibitor-induced emesis. Consistently, [sar(9), Met(O(2))(11)]-substance P (NK(1) receptor agonist, 6 .mu.g i.c.v.) reduced the duration of anaesthesia induced by xylazine/ketamine. 5. In summary, this model is functionally coupled to PDE4, specific to alpha(2)-adrenoceptors and relevant to PDE4 inhibitor-induced emesis. It therefore provides a novel way of evaluating the emetic potential of PDE4 inhibitors in rats.

AN 2002044152 EMBASE

TI Assessing the emetic potential of PDE4 inhibitors in rats.

AU Robichaud A.; Savoie C.; Stamatiou P.B.; Lachance N.; Jolicoeur P.; Rasori R.; Chan C.C.

CS A. Robichaud, Merck Frosst Ctr. for Therap. Res., P.O. Box 1005, Pointe-Claire, Que. H9R 4P8, Canada. annette_robichaud@merck.com

SO British Journal of Pharmacology, (2002) 135/1 (113-118).
Refs: 26
ISSN: 0007-1188 CODEN: BJPCBM

CY United Kingdom

DT Journal; Article

FS 024 Anesthesiology
030 Pharmacology
037 Drug Literature Index
052 Toxicology

LA English

SL English

AB . . . kg(-1)), like MK-912 (alpha(2)-adrenoceptor antagonist: 0.01-3 mg kg(-1)), dose-dependently reduced the duration of anaesthesia. In contrast, vinpocetine (PDE1 inhibitor), EHNA (**PDE2 inhibitor**), milrinone (PDE3 inhibitor) and zaprinast (PDE5 inhibitor) had no significant effect at the doses tested (1-10 mg kg(-1)).
Analysis of. . .

CT Medical Descriptors:
*vomiting: . . . mechanism
anesthesia
anesthetic recovery
dose response
drug effect
drug blood level
drug cerebrospinal fluid level
drug absorption
drug distribution
nonhuman
male
rat
animal experiment
animal model
controlled study

article
priority journal
*phosphodiesterase IV inhibitor: CM, drug comparison
***phosphodiesterase IV inhibitor: CR, drug concentration**
*phosphodiesterase IV inhibitor: DO, drug dose
*phosphodiesterase IV inhibitor: IT, drug interaction
*phosphodiesterase IV inhibitor: TO, drug toxicity
*phosphodiesterase IV inhibitor: PK, pharmacokinetics
*phosphodiesterase IV inhibitor: SC, subcutaneous drug administration
alpha 2 adrenergic receptor blocking agent: CM, drug comparison
alpha 2 adrenergic receptor blocking agent: CR, drug concentration
alpha 2 adrenergic receptor blocking agent: DO, drug dose
alpha 2 adrenergic receptor blocking. . . IT, drug interaction
xylazine: IM, intramuscular drug administration
ketamine: DO, drug dose
ketamine: IT, drug interaction
ketamine: IM, intramuscular drug administration
phosphodiesterase inhibitor: CM, drug comparison
phosphodiesterase inhibitor: CR, drug concentration
phosphodiesterase inhibitor: DO, drug dose
phosphodiesterase inhibitor: IT, drug interaction
phosphodiesterase inhibitor: PK, pharmacokinetics
phosphodiesterase inhibitor: SC, subcutaneous drug administration
phosphodiesterase I inhibitor: CM, drug comparison
phosphodiesterase I inhibitor: CR, drug concentration
phosphodiesterase I inhibitor: DO, drug dose
phosphodiesterase I inhibitor: IT, drug interaction
phosphodiesterase I inhibitor: PK, pharmacokinetics
phosphodiesterase I inhibitor: SC, subcutaneous drug administration
phosphodiesterase II inhibitor: CM, drug comparison
phosphodiesterase II inhibitor: CR, drug concentration
phosphodiesterase II inhibitor: DO, drug dose
phosphodiesterase II inhibitor: IT, drug interaction
phosphodiesterase II inhibitor: PK, pharmacokinetics
phosphodiesterase II inhibitor: SC, subcutaneous drug administration
phosphodiesterase III inhibitor: CM, drug comparison
phosphodiesterase III inhibitor: CR, drug concentration
phosphodiesterase III inhibitor: DO, drug dose
phosphodiesterase III inhibitor: IT, drug interaction
phosphodiesterase III inhibitor: PK, pharmacokinetics
phosphodiesterase III inhibitor: SC, subcutaneous drug administration
phosphodiesterase V inhibitor: CM, drug comparison
phosphodiesterase V inhibitor: CR, drug concentration
phosphodiesterase V inhibitor: DO, drug dose
phosphodiesterase V inhibitor: IT, drug interaction
phosphodiesterase V inhibitor: PK, pharmacokinetics
phosphodiesterase V inhibitor: SC, subcutaneous drug administration
6 (4 pyridylmethyl) 8 (3 nitrophenyl)quinoline: CM, drug comparison
6 (4 pyridylmethyl) 8 (3 nitrophenyl)quinoline: CR, drug concentration
6 (4 pyridylmethyl) 8 (3 nitrophenyl)quinoline: DO, drug dose
6 (4 pyridylmethyl) 8 (3. . . pyridylmethyl) 8 (3 nitrophenyl)quinoline: SC, subcutaneous drug administration
1,3,4,5',6,6',7,12b octahydro 1',3' dimethyl 2h spiro[benzo[b]furo[2,3 a]quinolizine 2,4' pyrimidine] 2' one: CM, drug comparison
1,3,4,5',6,6',7,12b octahydro 1',3' dimethyl 2h spiro[benzo[b]furo[2,3 a]quinolizine 2,4' pyrimidine] 2' one: CR, drug concentration
1,3,4,5',6,6',7,12b octahydro 1',3' dimethyl 2h spiro[benzo[b]furo[2,3 a]quinolizine 2,4'. . . 2' one: PK, pharmacokinetics

1,3,4,5',6,6',7,12b octahydro 1',3' dimethyl 2h spiro[benzo[b]furo[2,3 a]quinolizine 2,4' pyrimidine] 2' one: SC, subcutaneous drug administration
vinpocetine: CM, drug comparison
vinpocetine: CR, drug concentration
vinpocetine: DO, drug dose
vinpocetine: IT, drug interaction
vinpocetine: PK, pharmacokinetics
vinpocetine: SC, subcutaneous drug administration
9 (2 hydroxy 3 nonyl)adenine: CM, drug comparison
9 (2 hydroxy 3 nonyl)adenine: CR, drug concentration
9 (2 hydroxy 3 nonyl)adenine: DO, drug dose
9 (2 hydroxy 3 nonyl)adenine: IT, drug interaction
9 (2 hydroxy 3 nonyl)adenine: PK, pharmacokinetics
9 (2 hydroxy 3 nonyl)adenine: SC, subcutaneous drug administration
milrinone: CM, drug comparison
milrinone: CR, drug concentration
milrinone: DO, drug dose
milrinone: IT, drug interaction
milrinone: PK, pharmacokinetics
milrinone: SC, subcutaneous drug administration
zaprinast: CM, drug comparison
zaprinast: CR, drug concentration
zaprinast: DO, drug dose
zaprinast: IT, drug interaction
zaprinast: PK, pharmacokinetics
zaprinast: SC, subcutaneous drug administration
pentobarbital: DO, drug dose
pentobarbital: IT, drug. . .

L4 ANSWER 5 OF 7 MEDLINE DUPLICATE 1
AB The aim of this study was to investigate the role of the inhibitors of different PDE isoenzymes (PDE 1-5) on the production of two pro-inflammatory cytokines - tumor necrosis factor alpha (TNF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Two in vitro models were used to compare the antiinflammatory properties of PDE inhibitors with that of glucocorticoids. The effect on TNF release from diluted human blood following lipopolysaccharide (LPS from Salmonella abortus equi) stimulation as well as the GM-CSF and TNF release from human nasal polyp cells following allergic stimulation were investigated. Both models proofed to be well suited for the characterisation of the antiinflammatory properties of new chemical entities.In diluted human blood and dispersed human nasal polyp cells the induced TNF release was most potently suppressed by selective PDE4 inhibitors. Amrinone and milrinone, selective PDE3 inhibitors, suppressed TNF secretion to a lesser extent. The effects of theophylline (unspecific PDE inhibitor), vinpocetine (PDE1 inhibitor), EHNA (**PDE2 inhibitor**) and the PDE5 inhibitors zaprinast and E 4021 were weak. In human blood, the tested glucocorticoids beclomethasone, dexamethasone and fluticasone inhibited the LPS induced TNF release potently in a **concentration** dependent manner, whereas in dispersed human nasal polyp cells, the effect of the glucocorticoids on allergically induced TNF release, with the exception of dexamethasone, was much less pronounced. Glucocorticoids were the most potent inhibitors of GM-CSF release and the effect correlates well with the affinity to the glucocorticoid receptor. The selective PDE 4

inhibitors, and to a certain extent the PDE3 inhibitors amrinone and milrinone, reduced the GM-CSF release in a **concentration** dependent manner. In all investigations selective PDE4 inhibitors reduced TNF release to a much higher degree (4-10 fold) than GM-CSF release. Copyright 2002 Elsevier Science Ltd.

AN 2002233225 IN-PROCESS

DN 21967809 PubMed ID: 11969359

TI Modulation of TNF and GM-CSF Release from Dispersed Human Nasal Polyp Cells and Human Whole Blood by Inhibitors of Different PDE Isoenzymes and Glucocorticoids.

AU Marx Degenhard; Tassabehji Mahmoud; Heer Sabine; Huttenbrink K-B; Szelenyi Istvan

CS Arzneimittelwerk Dresden GmbH, Pulmonary Pharmacology, Corporate Research ASTA Medica AG, Radebeul, Germany.

SO PULMONARY PHARMACOLOGY AND THERAPEUTICS, (2002) 15 (1) 7-15. Journal code: 9715279. ISSN: 1094-5539.

CY England: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS IN-PROCESS; NONINDEXED; Priority Journals

ED Entered STN: 20020424
Last Updated on STN: 20020424

AB . . . PDE3 inhibitors, suppressed TNF secretion to a lesser extent. The effects of theophylline (unspecific PDE inhibitor), vinpocetine (PDE1 inhibitor), EHNA (**PDE2 inhibitor**) and the PDE5 inhibitors zaprinast and E 4021 were weak. In human blood, the tested glucocorticoids beclomethasone, dexamethasone and fluticasone inhibited the LPS induced TNF release potently in a **concentration** dependent manner, whereas in dispersed human nasal polyp cells, the effect of the glucocorticoids on allergically induced TNF release, with. . . PDE 4 inhibitors, and to a certain extent the PDE3 inhibitors amrinone and milrinone, reduced the GM-CSF release in a **concentration** dependent manner. In all investigations selective PDE4 inhibitors reduced TNF release to a much higher degree (4-10 fold) than GM-CSF. . .

L4 ANSWER 6 OF 7 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 2

AB The gut hormone, glucagon-like peptide-1 (GLP-1), which is secreted in nanomolar amounts in response to nutrients in the intestinal lumen, exerts cAMP/protein kinase A-mediated insulinotropic actions in target endocrine tissues, but its actions in heart cells are unknown. GLP-1 (10 nmol/L) increased intracellular cAMP (from 5.7.+-.0.5 to 13.1.+-.0.12 pmol/mg protein) in rat cardiac myocytes. The effects of cAMP-doubling **concentrations** of both GLP-1 and isoproterenol (ISO, 10 nmol/L) on contraction amplitude, intracellular Ca(2+) transient (CaT), and pH(i) in indo-1 and seminaphthorhodafluor (SNARF)-1 loaded myocytes were compared. Whereas ISO caused a characteristic increase (above baseline) in contraction amplitude (160.+-.34%) and CaT (70.+-.5%), GLP-1 induced a significant decrease in contraction amplitude (-27.+-.5%) with no change in the CaT after 20 minutes. Neither pertussis toxin treatment nor exposure to the cGMP-stimulated phosphodiesterase (**PDE2**) **inhibitor** erythro-9-(2-hydroxy-3-nonyl)adenine or the nonselective PDE inhibitor 3-isobutyl-1-methylxanthine nor the phosphatase inhibitors okadaic acid or calyculin A unmasked an ISO-mimicking response of GLP-1. In SNARF-1-loaded myocytes, however, both ISO and GLP-1 caused an intracellular acidosis (.DELTA.pH(i) -0.09.+-.0.02 and -0.08.+-.0.03,

respectively). The specific GLP-1 antagonist exendin 9-39 and the cAMP inhibitory analog Rp-8CPT-cAMPS inhibited both the GLP-1-induced intracellular acidosis and the negative contractile effect. We conclude that in contrast to .beta.-adrenergic signaling, GLP-1 increases cAMP but fails to augment contraction, suggesting the existence of functionally distinct adenylyl cyclase/cAMP/protein kinase A compartments, possibly determined by unique receptor signaling microdomains that are not controlled by pertussis toxin-sensitive G proteins or by enhanced local PDE or phosphatase activation. Furthermore, GLP-1 elicits a cAMP-dependent modest negative inotropic effect produced by a decrease in myofilament-Ca(2+) responsiveness probably resulting from intracellular acidification.

AN 2002058983 EMBASE

TI Glucagon-like peptide-1 increases cAMP but fails to augment contraction in adult rat cardiac myocytes.

AU Vila Petroff M.G.; Egan J.M.; Wang X.; Sollott S.J.

CS Dr. S.J. Sollott, Laboratory of Cardiovascular Science, Gerontology Research Center, National Institute on Aging, 5600 Nathan Shock Dr, Baltimore, MD 21224-6825, United States. sollotts@grc.nia.nih.gov

SO Circulation Research, (31 Aug 2001) 89/5 (445-452).
Refs: 47
ISSN: 0009-7330 CODEN: CIRUAL

CY United States

DT Journal; Article

FS 002 Physiology
003 Endocrinology
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology

LA English

SL English

AB . . . GLP-1 (10 nmol/L) increased intracellular cAMP (from 5.7.+-.0.5 to 13.1.+-.0.12 pmol/mg protein) in rat cardiac myocytes. The effects of cAMP-doubling **concentrations** of both GLP-1 and isoproterenol (ISO, 10 nmol/L) on contraction amplitude, intracellular Ca(2+) transient (CaT), and pH(i) in indo-1 and. . . (-27.+-.5%) with no change in the CaT after 20 minutes. Neither pertussis toxin treatment nor exposure to the cGMP-stimulated phosphodiesterase (**PDE2**) **inhibitor** erythro-9-(2-hydroxy-3-nonyl)adenine or the nonselective PDE inhibitor 3-isobutyl-1-methylxanthine nor the phosphatase inhibitors okadaic acid or calyculin A unmasked an ISO-mimicking response. . .

L4 ANSWER 7 OF 7 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 3

AB 1. The effects of several phosphodiesterase (PDE) inhibitors on the L-type Ca current (I(Ca)) and intracellular cyclic AMP **concentration** ([cAMP](i)) were examined in isolated rat ventricular myocytes. The presence of mRNA transcripts encoding for the different cardiac PDE subtypes was confirmed by RT-PCR. 2. IBMX (100 .mu.M), a broad-spectrum PDE inhibitor, increased basal I(Ca) by 120% and [cAMP](i) by 70%, similarly to a saturating **concentration** of the .beta.-adrenoceptor agonist isoprenaline (1 .mu.M). However, MIMX (1 .mu.M), a PDE1 inhibitor, EHNA (10 .mu.M), a **PDE2 inhibitor**, cilostamide (0.1 .mu.M), a PDE3 inhibitor, or Ro 20-1724 (0.1 .mu.M), a PDE4 inhibitor, had no effect on basal I(Ca) and little stimulatory effects on [cAMP](i) (20-30%). 3. Each selective PDE inhibitor was then tested in the presence of another inhibitor to examine whether a concomitant inhibition of two PDE subtypes had any effect on

I(Ca) or [cAMP](i). While all combinations tested significantly increased [cAMP](i) (40-50%), only cilostamide (0.1 .mu.M) + Ro20-1724 (0.1 .mu.) produced a significant stimulation of I(Ca) (50%). Addition of EHNA (10 .mu.M) to this mix increased I(Ca) to 110% and [cAMP](i) to 70% above basal, i.e. to similar levels as obtained with IBMX (100 .mu.M) or isoprenaline (1 .mu.M). 4. When tested on top of a sub-maximal **concentration** of isoprenaline (1 .mu.M), which increased I(Ca) by (.simeq. 40% and had negligible effecl on [cAMP](i), each selective PDE inhibitor induced a clear stimulation of [cAMP](i) and an additional increase in I(Ca). Maximal effects on I(Ca) were .simeq. 8% for MIMX (3 .mu.M), .simeq. 20% for EHNA (1-3 .mu.M), .simeq. 30% for cilostamide (0.3-1 .mu.M) and .simeq. 50% for Ro20-1724 (0.1 .mu.M). 5. Our results demonstrate that PDE1-4 subtypes regulate I(Ca) in rat ventricular myocytes. While PDE3 and PDE4 are the dominant PDE subtypes involved in the regulation of basal I(Ca), all four PDE subtypes determine the response of I(Ca) to a stimulus activating cyclic AMP production, with the
rank order of potency PDE4>PDE3>PDE2>PDE1.

AN 1999160968 EMBASE

TI Characterization of the cyclic nucleotide phosphodiesterase subtypes involved in the regulation of the L-type Ca2+ current in rat ventricular myocytes.

AU Verde I.; Vandecasteele G.; Lezoualac'h F.; Fischmeister R.

CS R. Fischmeister, Lab. Cardiologie Cellulaire Mol., INSERM U-446, Universite de Paris-Sud, F-92296 Chatenay-Malabry, France. Fisch@vjf.inserm.fr

SO British Journal of Pharmacology, (1999) 127/1 (65-74).
Refs: 41
ISSN: 0007-1188 CODEN: BJPCBM

CY United Kingdom

DT Journal; Article

FS 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB 1. The effects of several phosphodiesterase (PDE) inhibitors on the L-type
Ca current (I(Ca)) and intracellular cyclic AMP **concentration** ([cAMP](i)) were examined in isolated rat ventricular myocytes. The presence of mRNA transcripts encoding for the different cardiac PDE subtypes. . . IBMX (100 .mu.M), a broad-spectrum PDE inhibitor, increased basal I(Ca) by 120% and [cAMP](i) by 70%, similarly to a saturating **concentration** of the .beta.-adrenoceptor agonist isoprenaline (1 .mu.M). However, MIMX (1 .mu.M), a PDE1 inhibitor, EHNA (10 .mu.M), a **PDE2 inhibitor**, cilostamide (0.1 .mu.M), a PDE3 inhibitor, or Ro 20-1724 (0.1 .mu.M), a PDE4 inhibitor, had no effect on basal I(Ca). . . similar levels as obtained with IBMX (100 .mu.M) or isoprenaline (1 .mu.M). 4. When tested on top of a sub-maximal **concentration** of isoprenaline (1 .mu.M), which increased I(Ca) by (.simeq. 40% and had negligible effecl on [cAMP](i), each selective PDE inhibitor. . .

=>